DESCRIPTION

Novel use of cannabinoid receptor agonist

Techinical Field

The present invention relates to an inhibitor for inflammatory cell infiltration in the respiratory tract, an inhibitor for hyperirritability in the respiratory tract, a muciparous inhibitor, or a bronchodilator which contains a compound having a cannabinoid receptor agonistic acitivity as an active ingredient.

Background Art

In Patent 1 and Non-Patent 1, it is described that (R)-methanandamide which is a cannabinoid receptor modulator and a cannabinoid receptor agonist, exhibits an inhibitory activity for hyperirritability in the respiratory tract. Furthermore, in Non-Patent 1, 2, 3, 4, and 5, it is described that cannabinoid, anandamide, nabilone, and CP55,940, which are cannabinoid receptor agonists exhibit an inhibitory activity for constriction of bronchial plain muscle. However, an inhibitory activity for inflammatory cell infiltration in the respiratory tract and a muciparous inhibitory activity are not described in the literatures. In Patent 2, it is described that a cannabinoid receptor agonist exhibits preventing effect and/or treating effect for asthma. Furthermore, in Patent 3, it is described that a cannabinoid receptor agonist exhibits treating effect for espiratory illness.

As a cannabinoid receptor agonist, are disclosed quinoline derivatives in Patent 4 and Patent 5, thiazine derivatives in Patent 6 and Patent 7, pyridone derivatives in Patent 8 and the like.

Patent 1: WO03/061699

Patent 2: WO02/10135

Patent 3: WO04/000807

Patent 4: WO99/02499

Patent 5: WO00/40562

Patent 6: WO01/19807

Patent 7: WO02/072562

Patent 8: WO02/053543

Non-Patent 1: British Journal of Pharmacology, 2001, 134(4), 771-776

Non-Patent 2: Journal of Cannabis Therapeutics, 2002, 2(1), 59-71

Non-Patent 3: Marihuana and Medicine, New York, 1999, Mar. 20-21, 1998

Non-Patent 4: Pharmacol. Marihuna, 1976, 1, 269-276

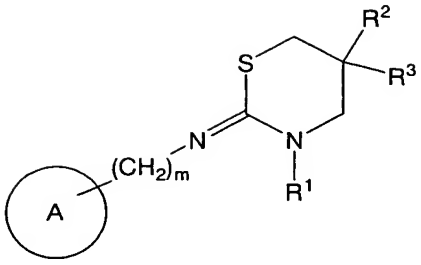
Non-Patent 5: American Review of Respivatory Disease

Disclosure of Invention

The object of the present invention is to provide an inhibitor for inflammatory cell infiltration in the respiratory tract, an inhibitor for hyperirritability in the respiratory tract, a muciparous inhibitor, or a bronchodilator which contains as an active ingredient a compound having a cannabinoid receptor agonistic acitivity.

The inventors of the present invention have found that the cannabinoid receptor agonist as shown below exhibits strong effect as an inhibitor for inflammatory cell infiltration in the respiratory tract, an inhibitor for hyperirritability in the respiratory tract, a muciparous inhibitor, or a bronchodilator.

The present invention relates to 1) an inhibitor for inflammatory cell infiltration in the respiratory tract, an inhibitor for hyperirritability in the respiratory tract, a muciparous inhibitor, or a bronchodilator which contains as an active ingredient a compound represented by the formula (I):



(I)

wherein R^1 is the group represented by the formula: -C(=Z)-W-R^4 wherein Z is a oxygen atom or a sulfur atom; W is a oxygen atom or a sulfur atom; R^4 is optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl;

R^2 and R^3 are independently optionally substituted alkyl or optionally substituted cycloalkyl; or

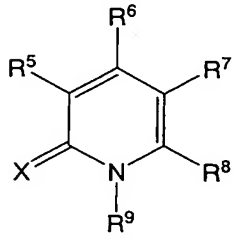
R^2 and R^3 are taken together to form alkylene which may contain an optionally substituted heteroatom(s);

m is an integer of 0 to 2;

A is optionally substituted aryl or optionally substituted heteroaryl,

2) An inhibitor for inflammatory cell infiltration in the respiratory tract, an inghibitor for hyperirritability in the respiratory tract, a muciparous inhibitor, or a bronchodilator according to 1) wherein R^1 is the group represented by the formula: -C(=Z)-W-R^4 wherein Z is a oxygen atom or a sulfur atom; W is a sulfur atom; R^4 is optionally substituted alkyl or alkenyl; R^2 and R^3 are independently alkyl; or R^2 and R^3 taken together may form optionally substituted alkylene; m is 0; A is aryl optionally substituted with one or two substitutent(s) selected from the group consisting of alkyl, haloalkyl, hydroxy, alkoxy, haloalkoxy, alkylthio, and haloalkylthio,

3) An inhibitor for inflammatory cell infiltration in the respiratory tract, an inhibitor for hyperirritability in the respiratory tract, a muciparous inhibitor, or a bronchodilator which contains as an active ingredient a compound represented by the formula (II):



(II)

wherein R^5 is the group represented by the formula: -Y^1-Y^2-Y^3-R^a wherein Y^1 and Y^3 are

each independently a bond or optionally substituted alkylene; Y^2 is a bond, -O-, -O-SO_2-, -NR^b-, -NR^b-C(=O)-, -NR^b-SO_2-, -NR^b-C(=O)-O-, -NR^b-C(=O)-NR^b-, -NR^b-C(=S)-NR^b-, -S-, -C(=O)-O-, or -C(=O)-NR^b-; R^a is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkylnyl, an optionally substituted carbocyclic group, an optionally substituted heterocyclic group, or acyl; R^b is each independently a hydrogen atom, optionally substituted alkyl, or acyl;

R^6 is a hydrogen atom, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkylnyl, a halogen atom, or alkoxy;

R^7 and R^8 are each independently a hydrogen atom, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkylnyl, a halogen atom, optionally substituted phenyl, or optionally substituted carbamoyl; or

R^7 and R^8 are taken together with the adjacent carbon atoms to form a 5 to 8 membered ring which may contain a heteroatom(s) and /or an unsaturated bond(s);

R^9 is a hydrogen atom, optionally substituted alkyl which may contain a heteroatom(s) and /or an unsaturated bond(s), or the group represented by the formula -Y^6-R^e wherein Y^6 is a bond, optionally substituted alkylene, alkenylene, alkylnylene, -O-, -S-, -SO-, or -SO_2-; R^e is an optionally substituted carbocyclic group or an optionally substituted heterocyclic group;

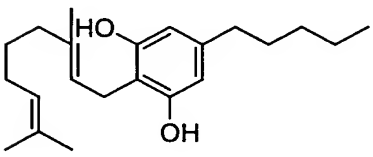
X is a oxygen atom or a sulfur atom,

4) An inhibitor for inflammatory cell infiltration in the respiratory tract, an inhibitor for hyperirritability in the respiratory tract, a muciparous inhibitor, or a bronchodilator according to 3) wherein R^5 is the group represented by the formula: -Y^1-Y^2-Y^3-R^a wherein Y^1 is a bond; Y^2 is -C(=O)-NH-; Y^3 is a bond or optionally substituted alkylene; R^a is an optionally substituted carbocyclic group; R^6 is a hydrogen atom; R^7 is alkyl, a halogen atom, or optionally substituted phenyl; R^8 is a hydrogen atom or alkyl; or R^7 and R^8 are taken together with the adjacent carbon atoms to form a 8 membered ring which may contain an unsaturated bond(s); R^9 is optionally substituted C3 or more alkyl which may contain a heteroatom(s) and /or an unsaturated bond(s), or the group represented by the formula -Y^6-R^e wherein Y^6 is a bond or optionally substituted alkylene; R^e is an optionally substituted carbocyclic group,

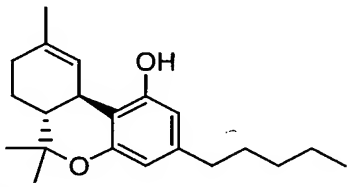
5) Use of a compounds represented by the formula (I) in 1) or (II) in 3) for preparation of a pharmaceutical composition for preventing and/or treating an inflammatory cell infiltration in the respiratory tract, a hyperirritability in the respiratory tract, a muciparous, or a bronchoconstrictive action,

6) A method for preventing and/or treating a mammal, including a human, to alleviate the pathological effects of an inflammatory cell infiltration in the respiratory tract, a hyperirritability in the respiratory tract, a muciparous, or a bronchoconstrictive action wherein the method comprises administration to said mammal of a compound represented by the formula (I) in 1) or (II) in 3) in a pharmaceutically effective amount.

In the present specification, "cannabinoid" is a general term including about 30 compounds having the fundamental skeleton represented by the formula (III) wherein is two isoprene groups bonds with 5-pentylresorcinol which is included in an amulet at 2-position, cyclization derivatives thereof, oxidation derivatives thereof, and a transformation derivatives thereof. Examples are the following Δ^9-tetrahydrocannabinol and the like.



(III)



Δ^9-tetrahydrocannabinol

The meaning of each term are shown as follows. Each term is used to express the same meaning employed alone or in combination with other terms in the specification.

In the present specification, the term "halogen atom" means fluorine atom, chlorine atom, bromine atom, and iodine atom.

The term "alkyl" includes a straight- or branched chain C1-C10 alkyl. Examples are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-

pentyl, isopentyl, neo-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, and the like. Especially, preferable is a straight- or branched chain C1-C4 alkyl, for example, preferable are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, or t-buty.

The term "alkenyl" includes a straight- or branched chain C2-C8 alkenyl which is the above-mentioned "alkyl" substituted with one or more double bond. Examples are viny, 1-propenyl, allyl, isopropenyl, 1-buteneyl, 2-buteneyl, 3-buteneyl, 3-pentenyl, 1,3-butadienyl, 3-methyl-2-butenyl, and tke like. Especially, preferable is a straight- or branched chain C2-C4 alkenyl, for example, preferable are allyl, isopropenyl, or 3-buteneyl.

The term "alkynyl" includes a straight- or branched chain C2-C8 alkynyl which is the above-mentioned "alkyl" substituted with one or more triple bond. Examples are ethynyl, propargyl, and tke like. Especially, preferable is a straight- or branched chain C2-C4 alkynyl, for example, preferable is propargyl.

The term "haloalkyl" means the above-mentioned "alkyl" substituted with one or more halogen atom(s). Example are chloromethyl, dichloromethyl, difluoromethyl, trifluoromethyl, chloroethyl (e.g. 2-chloroethyl), dichloroethyl (e.g., 1,2-dichloroethyl, 2,2-chloroethyl), chloropropyl (e.g., 2- chloropropyl, 3-chloropropyl), and the like. Preferable is haloC1-C3 alkyl.

The term "alkylene" includes straight- or branched chain C1-C10 alkylene. Examples are methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene, 1-methylethylene, 1-ethylethylene, 1-dimethylethylene, 1,2-dimethylethylene, 1,1-diethylethylene, 1,2-diethylethylene, 1-ethyl-2-methylethylene, 1-methyltrimethylene, 2-methyltrimethylene, 1,1-dimethyltrimethylene, 1,2-dimethyltrimethylene, 2,2-dimethyltrimethylene, 1-ethyltrimethylene, 2-ethyltrimethylene, 1,1-diethyltrimethylene, 1,2-diethyltrimethylene, 2,2-diethyltrimethylene, 2-ethyl-2-methyltrimethylene, 2,2-di-n-

propyltrimethylene, 1-methyltetramethylene, 2-methyltetramethylene, 1,1-dimethyltetramethylene, 1,2-dimethyltetramethylene, 2,2-dimethyltetramethylene, 3,3-dimethylpentamethylene, and the like. Especially, preferable is a straight- or branched chain C1-C6 alkylene, for example, preferable are methylene, ethylene, trimethylene, tetramethylene, pentamethylene, or hexamethylene.

Alkylene (e.g., methylene, ethylene, trimethylene, tetramethylene, pentamethylene), cycloalkyl (e.g., cyclopropyl, cyclo, trimethylene, tetramethylene, pentamethylene), alkoxy (e.g., methoxy, ethoxy), alkylthio (e.g., methylthio, ethylthio), alkylamino (e.g., methylamino, ethylamino, dimethylamino), acylamino (e.g., acetylamino), aryl (e.g., phenyl), aryloxy (e.g., phenoxy), halogen (e.g., fluoro, chloro, bromo, iodo), hydroxy, amino, nitro, alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl), arylsulfonyl (e.g., benzensulfonyl), cyano, hydroxyamino, carboxy, alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl), acyl (e.g., acetyl, benzoyl), aralkyl (e.g., benzyl), mercapto, hydrazino, amidino, guanidino or the like is exemplified as the substituents of "optionally substituted alkylene". One to four of these substituents may substitute at any position.

Furthermore, alkylene substituted with alkylene includes alkylene substituted atom with alkylene via a spiro (e.g., 2,2-ethylenetrimethylene, 2,2-trimethylenetrimethylene, 2,2-tetramethylenetrimethylene, 2,2-pentamethylenetrimethylene), and alkylene substituted with alkylene at different position (e.g., 1,2-tetramethyleneethylene, 1,2-ethylenetrimethylene). For example, preferable are 2,2-ethylenetrimethylene, 2,2-trimethylenetrimethylene, 2,2-tetramethylenetrimethylene, and 2,2-pentamethylenetrimethylene. Especially, preferable are 2,2-ethylenetrimethylene, 2,2-tetramethylenetrimethylene, and 2,2-pentamethylenetrimethylene.

The term "alkylene may contain a heteroatom(s)" includes straight- and branched chain C2-C10 alkylene which may contain optionally substituted one to three heteroatom(s). Examples are ethylene, trimethylene, tetramethylene,

pentamethylene, methylenedioxy, ethylenedioxy, ethyleneoxyethylene, and the like. Especially, preferable is straight- C3-C5 alkylene may contain one heteroatom. Tetramethylene, pentamethylene, ethyleneoxyethylene, ethyleneaminoethylene, and ethylenethioethylene are exemplified .

The term "alkenylene" includes straight- or branched chain C2-C12 alkenylene which is the above-mentioned "alkylene" having one or more double bond(s). Examples are vinylene, propenylene, and butenylene. Preferable is straight- chain C2-C6 alkenylene. For example, vinylene, propenylene, butenylene, pentenylene, hexenylene, butadienylene, or the like.

The term "alkynylene" includes straight- or branched chain C2-C12 alkynylene which is the above-mentioned "alkylene" having one or more triple bond(s).

The term "a carbocyclic group" includes a cyclic group consisting of a carbon atom and a hydrogen atom. Further, "a carbocyclic group"may be a saturated ring or an unsaturated ring. Examples are the blow-mentioned "aryl", the blow-mentioned "cycloalkyl", the blow-mentioned "cycloalkenyl", and the like. Preferable is the group derived from a C3-C14 ring.

The term "cycloalkyl" includes C3-C10 saturated carbocyclic group. Examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. Preferable is C3-C6 cycloalkyl, and examples are cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

The term "cycloalkenyl" includes C3-C12 cycloalkenyl which is the above-mentioned "cycloalkyl" having one or more double bond(s). Examples are cyclopropenyl (e.g., 1-cyclopropenyl), cyclobutenyl (e.g., 1-cyclobutenyl), cyclopentenyl (e.g., 1-cyclopenten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl), cyclohexenyl (e.g., 1-cyclohexen-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl), cycloheptenyl (e.g., 1-

cycloheptenyl), cyclooctenyl (1-cyclooctenyl), and the like. Especially, preferable are 1-cyclohexen-1-yl, 2-cyclohexen-1-yl, and 3-cyclohexen-1-yl.

The term "aryl" includes a C6-C14 aryl, and examples are phenyl, naphthyl, anthryl, phenanthryl, and the like. Especially, preferable are phenyl and naphthyl.

The term "aralkyl" includes the above-mentioned "alkyl" substituted with the above-mentioned "aryl". Examples are benzyl, phenylethyl (e.g., 1-phenylethyl, 2-phenylethyl), phenylpropyl (e.g., 1-phenylpropyl, 2-phenylpropyl, 3-phenylpropyl), naphthylmethyl (e.g., 1-naphthylmethyl, 2-naphthylmethyl), and the like. Especially, preferable are benzyl and naphthylmethyl.

The term "heteroaryl" includes a C1-C9 heteroaryl having one to four nitrogen atom(s), oxygen atom(s) and/or sulfur atom(s). Examples are furyl (e.g., 2-furyl, 3-furyl), thienyl (e.g., 2-thienyl, 3-thienyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), triazolyl (e.g., 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-4-yl), tetrazolyl (e.g., 1-tetrazolyl, 2-tetrazolyl, 5-tetrazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), thiazolyl(e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), thiadiazolyl, isothiazolyl (e.g., 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl), furazanyl (e.g., 3-furazanyl), pyrazinyl (e.g., 2-pyrazinyl), oxadiazolyl (e.g., 1,3,4-oxadiazol-2-yl), benzofuryl (e.g., 2-benzo[b]furyl, 3-benzo[b]furyl, 4-benzo[b]furyl, 5-benzo[b]furyl, 6-benzo[b]furyl, 7-benzo[b]furyl), benzothienyl (e.g., 2-benzo[b]thienyl, 3-benzo[b]thienyl, 4-benzo[b]thienyl, 5-benzo[b]thienyl, 6-benzo[b]thienyl, 7-benzo[b]thienyl), benzimidazolyl (e.g., 1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl), dibenzofuryl, benzoxazolyl, quinoxalinyl (e.g., 2-quinoxalinyl, 5-quinoxalinyl, 6-quinoxalinyl), cinnolinyl (e.g., 3-cinnolinyl, 4-cinnolinyl, 5-cinnolinyl, 6- cinnolinyl, 7-cinnolinyl, 8-cinnolinyl),

quinazolinyl (e.g., 2-quinazolinyl, 4-quinazolinyl, 5-quinazolinyl, 6-quinazolinyl, 7-quinazolinyl, 8-quinazolinyl), quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl), phthalazinyl (e.g., 1-phthalazinyl, 5-phthalazinyl, 6-phthalazinyl), isoquinolyl (e.g., 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, 8-isoquinolyl), puryl, pteridinyl (e.g., 2-pteridinyl, 4-pteridinyl, 6-pteridinyl, 7-pteridinyl), carbazolyl, phenanthridinyl, acridinyl (e.g., 1-acridinyl, 2-acridinyl, 3-acridinyl, 4-acridinyl, 9-acridinyl), indolyl (e.g., 1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), isoindolyl, phenazinyl (e.g., 1-phenazinyl, 2-phenazinyl) or phenothiadinyl (e.g., 1-phenothiadinyl, 2-phenothiadinyl, 3- phenothiadinyl, 4-phenothiadinyl), and the like.

The term "a heterocyclic group" includes the group derived from a C1-C14 mono cyclic ring having one to four nitrogen atom(s), oxygen atom(s) and/or sulfur atom(s) and the group derived from a condensed ring which are combined two to three c rings. For example, "a heterocyclic group" includes the above-mentioned “heteroaryl” and the below-mentioned “non-heteroaryl”.

The term "non-heteraryl" includes a C1-C9 non-aromatic ring having one to four nitrogen atom(s), oxygen atom(s) and/or sulfur atom(s). Examples are 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidino, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-imidazolinyl, 2-imidazolinyl, 4-imidazolinyl, 1-imidazolidinyl, 2-imidazolidinyl, 4-imidazolidinyl, 1-pyrazolinyl, 3-pyrazolinyl, 4-pyrazolinyl, 1-pyrazolidinyl, 3-pyrazolidinyl, 4-pyrazolidinyl, piperidino, 2-piperidyl, 3-piperidyl, 4-piperidyl, piperazino, 2-piperazinyl, 2-morpholinyl, 3-morpholinyl, morpholino, tetrahydropyranyl, and the like. Especially, preferable are morpholino, pyrrolidino, piperidino and piperazino.

The alkyl part of "alkoxy" is defined as the above "alkyl". Methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, t-butoxy, n-pentyloxy, n-hexyloxy, n-heptyloxy, n-octyloxy, and the like are exemplified as "alkoxy". Preferable

are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, i-butoxy, sec-butoxy and t-butoxy.

The alkenyl part of "alkenyloxy" is defined as the above "alkenyl". Vinyloxy, 1-propenyloxy, 2-propenyloxy, 1-butenyloxy, 2-butenyloxy, 3-butenyloxy, 1,3-butadienyloxy, 3-methyl-2-butenyloxy, and the like are exemplified as "alkenyloxy". Preferred is 2-propenyloxy and 1-butenyloxy.

The term "haloalkoxy" means the above "alkoxy" substituted with one or more halogen. Examples are dichloromethoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy (2,2,2-trifluoroethoxy), and the like. Especially, preferable are difluoromethoxy and trifluoromethoxy.

The term "aryloxy" includes an oxygen atom substituted with the above "aryl". Examples are phenoxy, naphthoxy (e.g., 1-naphthoxy, 2-naphthoxy), anthryloxy (e.g., 1-anthryloxy, 2-anthryloxy), phenanthryl (e.g., 1-phenanthryl, 2-phenanthryl) and the like. Especially, preferable are phenoxy and naphthoxy.

The term "alkoxyalkoxy" includes the above-mentioned "alkoxy" substituted with the above-mentioned "alkoxy". Examples are methoxymethoxy, ethoxymethoxy, n-propoxymethoxy, isopropoxymethoxy, 1-methoxyethoxy, 2-methoxyethoxy, and the like. Especially, preferable are 1-methoxyethoxy, 2-methoxyethoxy.

The term "alkylthioalkoxy" includes the above-mentioned "alkoxy" substituted with the below-mentioned "alkylthio". Examples are methylthiomethoxy, ethylthiomethoxy, n-propylthiomethoxy, isopropylthiomethoxy, 1-methylthioethoxy, 2-methylthioethoxy, and the like. Especially, preferable are 1-methylthioethoxy and 2-methylthioethoxy.

The alkyl part of "alkylthio" is defined as the above-mentioned "alkyl".

Examples are methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio, t-butylthio, n-pentylthio, n-hexylthio and the like. Especially, preferable is C1-C4 straight- or branched chain alkylthio. For example, methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, i-butylthio, sec-butylthio, and t-butylthio are exemplified.

The term "haloalkylthio" means the above "alkylthio" substituted with one or more halogen. Examples are dichloromethylthio, difluoromethylthio, trifluoromethylthio, trifluoroethylthio (2,2,2-trifluoroethylthio) and the like. Preferable are difluoromethylthio and trifluoromethylthio.

Non-substituted amino, alkylamino (e.g., methylamino, ethylamino, n-propylamino, i-propylamino, dimethylamino, diethylamino, ethylmethylamino, propylmethylamino), acylamino (e.g., acetylamino, formylamino, propionylamino, benzoylamino), acylalkylamino (e.g., N-acethylmethylamino), aralkylamino (e.g., benzylamino, 1-phenylethylamino, 2-phenylethylamino, 1-phenylpropylamino, 2-phenylpropylamino, 3-phenylpropylamino, 1-naphthylmethylamino, 2-naphthylmethylamino, dibenzylamino), alkylsulfonylamino (e.g., methanesulfonylamino, ethanesulfonylamino), alkenyloxysulfonylamino (e.g., vinyloxysulfonylamino, allyloxysulfonylamino), alkoxycarbonylamino (e.g., methoxycaronylamino, ethoxycaronylamino, t-butoxycaronylamino), alkenylamono (e.g., vinylamino, allylamino), arylcarbonylamino (e.g., benzoylamino), and heteroarylcarbonylamino (e.g., pyridinecarboylamino) are exemplified as "optionally substituted amino".

The term "aralkylamino" means amino substituted with one or two the above-mentioned "aralkyl". Examples are benzylamino, phenylethylamino (e.g., 1-phenylethylamino, 2-phenylethylamino), phenylpropylamino (e.g., 1-phenylpropylamino, 2-phenylpropylamino, 3-phenylpropylamino), naphthylamino (e.g., 1-naphthylamin, 2-naphthylamin), dibenzylamino, and the like.

The term "acyl" means carbonyl substituted with the group except for a hydrogen atom. Examples are alkylcarbonyl (e.g., acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloryl, hexanoyl, octanoyl, lauroyl), alkenylcarbonyl (e.g., acryloyl, methacryloyl), cycloalkylcarbonyl (e.g., cyclopropanecarbonyl, cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl), arylcarbonyl (e.g., benzoyl, naphthoyl), and heteroarylcarbonyl (e.g., pyridinecarbonyl). These groups may be substuituted with alkyl, a halogen atom, or the like. Toluoyl which is an example of arylcarbonyl substituted with alkyl and trifluoroacetyl which is an example of alkylcarbonyl substituted with halogen atom are exemplified.

The term "alkoxycarbonyl" means carbonyl substituted with the above-mentioned "alkoxy". Examples are methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, i-propoxycarbonyl, n-butoxycarbonyl, i-butoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, n-pentyloxycarbonyl, n-hexyloxycarbonyl, n-heptyloxycarbonyl, n-hexyloxycarbonyl, n-heptyloxycarbonyl, n-octyloxycarbonyl, and the like. Preferable are methoxycarbonyl, ethoxycarbonyl and the like.

Alkyl (e.g., methyl, ethyl, n-propyl, i-propyl), acyl (e.g., formyl, acetyl, propionyl, benzoyl) and the like are exemplified as the substituents of "optionally substituted carbamoyl". The nitrogen atom of a carbamoyl group may be mono- or di- substituted with these substituents. Preferable are carbmoyl, N-methyl carbmoyl, N-ethyl carbmoyl, and the like as "optionally substituted carbamoyl".

The alkyl part of "alkylsulfonyl" is defined as the above-mentioned "alkyl". Methanesulfonyl, ethanesulfonyl and the like are exemplified as "alkylsulfonyl".

When "optionally substituted aralkyloxy", "optionally substituted aralkylthio", "optionally substituted aralkylamino", "optionally substituted phenyl", "optionally substituted aryl", "optionally substituted heteroaryl", "optionally substituted

heteroaryl", "an optionally substituted heterocyclic group", "optionally substituted alkyl", "optionally substituted alkenyl", "optionally substituted alkynyl", "optionally substituted alkoxyalkyl", "optionally substituted cycloalkyl", "an optionally substituted carbocyclic group", "alkylene which may contain optionally substituted a heteroatom(s)", or "optionally substituted alkyl which may contain optionally substituted a heteroatom(s) and/or an unsubstituted bond(s)" has substituent(s), each one to four of these substituents may substitute at any position.

Hydroxy, carboxy, halogen atom (fluorine atom, chlorine atom, bromine atom, iodine atom), haloalkyl (e.g., CF_3, CH_2CF_3, CH_2CCl_3), haloalkoxy, alkyl (e.g., methyl, ethyl, isopropyl, tert-butyl), alkenyl (e.g., vinyl), formyl, acyl (e.g., acetyl, propionyl, butyryl, pivoloyl, benzoyl, pyridinecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl), alkynyl (e.g., ethynyl), cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy), alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl), nitro, nitroso, oxo, optionally substituted amino (e.g., amino, alkylamino (e.g., methylamino, ethylamino, dimethylamino), formylamino, acylamino (e.g., acetylamino, benzoylamino), aralkylamino (e.g., benzylamino, tritylamino), hydroxyamino, alkylsulfonylamino, alkenyloxycarbonylamino, alkoxycarbonylamino, alkenylamino, arylcarbonylamino, heteroarylcarbonylamino), azido, aryl (e.g., phenyl), aryloxy (e.g., phenoxy), aralkyl (e.g., benzyl, phenethyl, phenylpropyl), alkylenedioxy (e.g., methylenedioxy), alkylene (e.g., methylene, ethylene, trimethylene, teteramethylene, pentamethylene), alkenylene (e.g., propenylene, butenylene, butadienylen), cyano, isocyano, isocyanato, thiocyanato, isothiocyanato, mercapto, alkylthio (e.g., methylthio, ethylthio), alkylsulfonyl (e.g., omethanesulfonyl, ethanesulfonyl), arylsuslfonyl (e.g., benzensulfonyl), optionally substituted carbamoyl, sulfamoyl, formyloxy, haloformyl, oxalo, thioformyl, thiocarboxy, dithiocarboxy, thiocarbamoyl, sulfino, sulfo, sulfoamino, hydrazino, ureido, amidino, guanidino, alkylsulfonyloxy, trialkylsilyl, haloalkylcarbonyloxy, formyloxy, acylthio, thioxo, alkoxyalkoxy, alkylthioalkoxy, and the like are exemplified as their substituents.

Preferable are oxo, hydroxy, alkenylene (e.g., propenylene, butenylene, butadienylene), acyl (e.g., acetyl, propionyl, pivaloyl, benzoyl, pyridinecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl), aralkyl (e.g., benzyl), alkylene (e.g., methylene, ethylene, trimethylene, tetramethlene, pentamethylene), and the like as the substituents of "5-8 menbered ring which may contain a heteroatom(s) and/or an unsaturated bond(s)"

Substsituents groups (Ia) to (Im) are shown as preferable substituent(s) groups for R^1 to R^3, m, and A of the compound represented by general formula (I).

R^1: (Ia) -C(=S)-S-R^4 or -C(=O)-S-R^4 wherein R^4 is optionally substituted alkyl or optionally substituted alkenyl, (Ib) -C(=S)-S-R^4 or -C(=O)-S-R^4 wherein R^4 is optionally substituted alkyl, (Ic) -C(=S)-S-R^4 wherein R^4 is optionally substituted alkyl.

R^2: (Id) optionally substituted alkyl, (Ie) alkyl.

R^3: (If) optionally substituted alkyl, (Ig) alkyl.

m: (Ih) 0.

A: (Ii) optionally substituted aryl or optionally substituted heteroaryl, (Ij) optionally substituted aryl, (Ik) optionally substituted heteroaryl.

Or, R^2 and R^3 are taken together to form (Il) alkylene which may contain optionally substituted alkylene, (Im) alkylene.

Examples of preferable group of the compound represented by general formula (I) contains [R^1, R^2, R^3, m, A]=[Ia, Id, If, Ih, Ii], [Ia, Id, If, Ih, Ij], [Ia, Id, If, Ih, Ik], [Ia, Id, Ig, Ih, Ii], [Ia, Id, Ig, Ih, Ij], [Ia, Id, Ig, Ih, Ik], [Ia, Ie, If, Ih, Ii], [Ia, Ie, If, Ih, Ij], [Ia, Ie, If, Ih, Ik], [Ia, Ie, Ig, Ih, Ii], [Ia, Ie, Ig, Ih, Ij], [Ia, Ie, Ig, Ih, Ik], [Ib, Id, If, Ih, Ii], [Ib, Id, If, Ih, Ij], [Ib, Id, If, Ih, Ik], [Ib, Id, Ig, Ih, Ii], [Ib, Id, Ig, Ih, Ij], [Ib, Id, Ig, Ih, Ik], [Ib, Ie, If, Ih, Ii], [Ib, Ie, If, Ih, Ij], [Ib, Ie, If, Ih, Ik], [Ib, Ie, Ig, Ih, Ii], [Ib, Ie, Ig, Ih, Ij], [Ib, Ie, Ig, Ih, Ik], [Ic, Id, If, Ih, Ii], [Ic, Id, If, Ih, Ij], [Ic, Id, If, Ih, Ik], [Ic, Id, Ig, Ih, Ii], [Ic, Id, Ig, Ih, Ij], [Ic, Id, Ig, Ih, Ik], [Ic, Ie, If, Ih, Ii], [Ic, Ie, If, Ih, Ij], [Ic, Ie, If, Ih, Ik], [Ic, Ie, Ig, Ih, Ii], [Ic, Ie, Ig, Ih, Ij], [Ic, Ie, Ig, Ih, Ik], or [R^1, R^2-R^3, m, A]=[Ia, Il, Ih, Ii], [Ia, Il, Ih, Ij], [Ia, Il, Ih,

Ik], [Ia, Im, Ih, Ii], [Ia, Im, Ih, Ij], [Ia, Im, Ih, Ik], [Ib, Il, Ih, Ii], [Ib, Il, Ih, Ij], [Ib, Il, Ih, Ik], [Ib, Im, Ih, Ii], [Ib, Im, Ih, Ij], [Ib, Im, Ih, Ik], [Ic, Il, Ih, Ii], [Ic, Il, Ih, Ij], [Ic, Il, Ih, Ik], [Ic, Im, Ih, Ii], [Ic, Im, Ih, Ij], [Ic, Im, Ih, Ik].

Substituents groups (IIa) to (IIm) are shown as preferable substituent(s) groups for R^5 to R^9, and X of the compound represented by general formula (II).

R^5: (IIa) -C(=O)-NH-Y^3-R^a wherein Y^3 is a bond or optionally substituted alkylene, R^a is optionally substituted alkyl, an optionally substituted carbocyclic group, or acyl, (IIb) -C(=O)-NH-Y^3-R^a wherein Y^3 is a bond or optionally substituted alkylene, R^a is an optionally substituted carbocyclic group, or acyl, (IIc) -C(=O)-NH-Y^3-R^a wherein Y^3 is a bond or optionally substituted alkylene, R^a is an optionally substituted carbocyclic group.

R^6: (IId) a hydrogen atom.

R^7: (IIe) a hydrogen atom or optionally substituted alkyl, (IIf) optionally substituted alkyl.

R^8: (IIg) a hydrogen atom or optionally substituted alkyl, (IIh) optionally substituted alkyl.

R^9: (IIi) optionally substituted alkyl or -Y^6-R^e wherein Y^6 is optionally substituted alkylene, R^e is an optinally substituted carbocyclic group, (IIj) optionally substituted alkyl.

X: (IIk) an oxygen atom.

Or, R^7 and R^8 are taken together with the adjacent carbon atom to form (Il) optionally substituted 5-8 membered ring, (Im) optionally substituted 8 membered ring, .

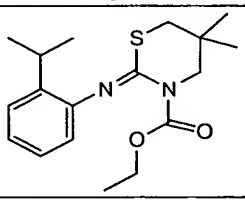
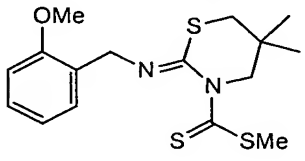
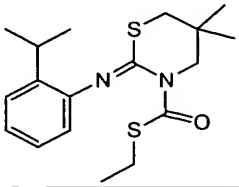
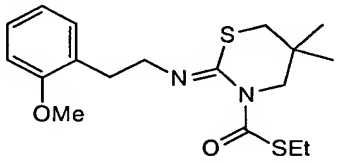
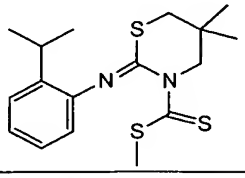
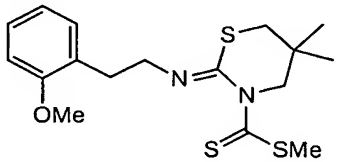
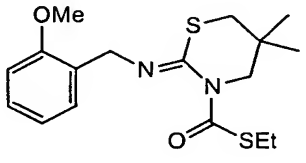
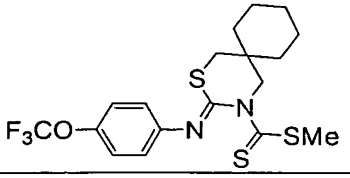
Examples of preferable group of the compound represented by general formula (II) contains [R^5, R^6, R^7, R^8, R^9, X]=[IIa, IId, IIe, IIg, IIi, IIk], [IIa, IId, IIe, IIg, IIj, IIk], [IIa, IId, IIe, IIh, IIi, IIk], [IIa, IId, IIe, IIh, IIj, IIk], [IIa, IId, IIf, IIg, IIi, IIk], [IIa, IId, IIf, IIg, IIj, IIk], [IIa, IId, IIf, IIh, IIi, IIk], [IIa, IId, IIf, IIh, IIj, IIk], [IIb, IId, IIe, IIg, IIi,

IIk], [IIb, IId, IIe, IIg, IIj, IIk], [IIb, IId, IIe, IIh, IIi, IIk], [IIb, IId, IIe, IIh, IIj, IIk], [IIb, IId, IIf, IIg, IIi, IIk], [IIb, IId, IIf, IIg, IIj, IIk], [IIb, IId, IIf, IIh, IIi, IIk], [IIb, IId, IIf, IIh, IIj, IIk], or [R^5, R^6, R^7-R^8, R^9, X]=[IIb, IId, IIl, IIi, IIk], [IIc, IId, IIe, IIg, IIi, IIk], [IIc, IId, IIe, IIg, IIj, IIk], [IIc, IId, IIe, IIh, IIi, IIk], [IIc, IId, IIe, IIh, IIj, IIk], [IIc, IId, IIf, IIg, IIi, IIk], [IIc, IId, IIf, IIg, IIj, IIk], [IIc, IId, IIf, IIh, IIi, IIk], [IIc, IId, IIf, IIh, IIj, IIk].

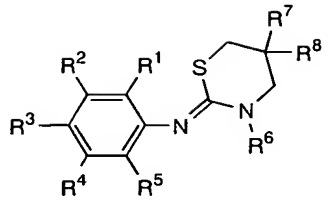
The term "solvate" means solvates of compounds of the present invention or the pharmaceutical acceptable salts thereof. Examples are monosolvate, disolvate, monohydrate, dihydrate, and the like are exemplified as "solvate".

The compounds described in WO 01/19807 or WO 02/072562 are exemplified as the compounds represented by the formula (I). Preferable are the compounds described in the following Tables.

[Table 1]

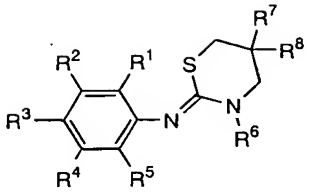
	Structure		Structure
I-3		I-9	
I-4		I-10	
I-5		I-11	
I-8		I-12	

[Table 2]



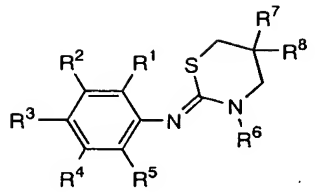
	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
I-16	H	H	H	H	H	COSEt	Me	Me
I-17	F	H	H	H	H	COSEt	Me	Me
I-18	Cl	H	H	H	H	COSEt	Me	Me
I-19	Me	H	H	H	H	COSEt	Me	Me
I-20	Et	H	H	H	H	COSEt	Me	Me
I-21	Pr	H	H	H	H	COSEt	Me	Me
I-22	Bu	H	H	H	H	COSEt	Me	Me
I-23	Bu^s	H	H	H	H	COSEt	Me	Me
I-24	Bu^t	H	H	H	H	COSEt	Me	Me
I-25	Ph	H	H	H	H	COSEt	Me	Me
I-26	CF_3	H	H	H	H	COSEt	Me	Me
I-27	OMe	H	H	H	H	COSEt	Me	Me
I-28	OEt	H	H	H	H	COSEt	Me	Me
I-29	OPr^i	H	H	H	H	COSEt	Me	Me
I-30	SMe	H	H	H	H	COSEt	Me	Me
I-31	SEt	H	H	H	H	COSEt	Me	Me
I-32	SPr^i	H	H	H	H	COSEt	Me	Me
I-33	NMe_2	H	H	H	H	COSEt	Me	Me
I-34	H	Pr^i	H	H	H	COSEt	Me	Me
I-35	H	H	Cl	H	H	COSEt	Me	Me
I-36	H	H	Pr^i	H	H	COSEt	Me	Me
I-37	H	H	NO_2	H	H	COSEt	Me	Me
I-38	Me	Me	H	H	H	COSEt	Me	Me
I-39	Me	H	Me	H	H	COSEt	Me	Me
I-40	Me	H	H	Me	H	COSEt	Me	Me
I-41	Me	H	H	H	Me	COSEt	Me	Me
I-42	H	Me	Me	H	H	COSEt	Me	Me
I-43	H	Me	H	Me	H	COSEt	Me	Me
I-44	Me	H	Cl	H	H	COSEt	Me	Me
I-45	Cl	H	Me	H	H	COSEt	Me	Me
I-46	Pr^i	H	NO_2	H	H	COSEt	Me	Me

[Table 3]



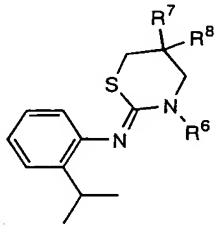
	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
I-47	Pr^i	H	H	H	NO_2	COSEt	Me	Me
I-48	NO_2	H	NO_2	H	H	COSEt	Me	Me
I-49	Pr	H	H	H	H	COSMe	Me	Me
I-50	Pr^i	H	H	H	H	COSMe	Me	Me
I-51	Bu^s	H	H	H	H	COSMe	Me	Me
I-52	H	Pr^i	H	H	H	COSMe	Me	Me
I-53	H	OMe	OMe	H	H	COSMe	Me	Me
I-54	H	-OCH_2O-		H	H	COSMe	Me	Me
I-55	H	OMe	OMe	OMe	H	COSMe	Me	Me
I-56	Et	H	H	H	H	CSSMe	Me	Me
I-57	Bu^s	H	H	H	H	CSSMe	Me	Me
I-58	CH_2OMe	H	H	H	H	CSSMe	Me	Me
I-59	CH(Me)OMe	H	H	H	H	CSSMe	Me	Me
I-60	OMe	H	H	H	H	CSSMe	Me	Me
I-61	OEt	H	H	H	H	CSSMe	Me	Me
I-62	SMe	H	H	H	H	CSSMe	Me	Me
I-63	SEt	H	H	H	H	CSSMe	Me	Me
I-64	SPr^i	H	H	H	H	CSSMe	Me	Me
I-65	SOMe	H	H	H	H	CSSMe	Me	Me
I-66	SO_2Me	H	H	H	H	CSSMe	Me	Me
I-67	SOEt	H	H	H	H	CSSMe	Me	Me
I-68	NMe_2	H	H	H	H	CSSMe	Me	Me
I-69	H	Pr^i	H	H	H	CSSMe	Me	Me
I-70	H	H	Cl	H	H	CSSMe	Me	Me
I-71	Me	H	Me	H	H	CSSMe	Me	Me
I-72	Me	H	H	Me	H	CSSMe	Me	Me
I-73	Me	H	H	H	Me	CSSMe	Me	Me
I-74	H	Me	Me	H	H	CSSMe	Me	Me
I-75	H	Me	H	Me	H	CSSMe	Me	Me
I-76	OMe	OMe	H	H	H	CSSMe	Me	Me
I-77	H	OMe	OMe	H	H	CSSMe	Me	Me
I-78	OMe	H	H	OMe	H	CSSMe	Me	Me

[Table 4]



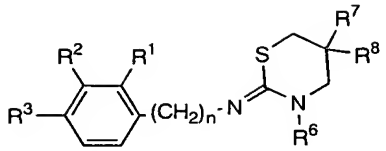
	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
I-79	OMe	H	OMe		H	CSSMe	Me	Me
I-80	H	-OCH_2O-		H	H	CSSMe	Me	Me
I-81	Pr^i	H	NO_2	H	H	CSSMe	Me	Me
I-82	Pr^i	H	H	H	NO_2	CSSMe	Me	Me
I-83	H	OMe	OMe	OMe	H	CSSMe	Me	Me
I-84	Pr^i	H	H	H	H	CSSEt	Me	Me
I-85	Bu^s	H	H	H	H	CSSEt	Me	Me
I-86	OEt	H	H	H	H	CSSEt	Me	Me
I-87	SMe	H	H	H	H	CSSEt	Me	Me
I-88	H	Pr^i	H	H	H	CSSEt	Me	Me
I-118	H	OEt	OEt	H	H	CSSMe	Me	Me
I-119	OMe	H	Me	H	H	CSSMe	Me	Me
I-120	OMe	H	H	Me	H	CSSMe	Me	Me
I-121	H	OMe	Me	H	H	CSSMe	Me	Me
I-122	Me	Me	H	H	H	CSSMe	Me	Me
I-123	N(Me)Ac	H	H	H	H	CSSMe	Me	Me

[Table 5]



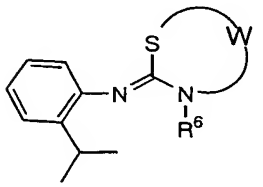
	R^6	R^7	R^8		R^6	R^7	R^8
I-90	COOMe	Me	Me	I-98	CSSPr	Me	Me
I-91	COOPr	Me	Me	I-99	$CSSPr^i$	Me	Me
I-96	CSOEt	Me	Me	I-100	CSSBn	Me	Me

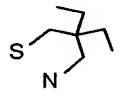
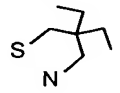
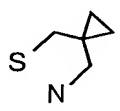
[Table 6]



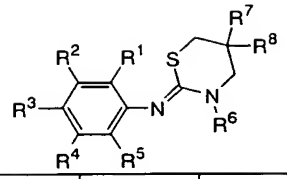
	R^1	R^2	R^3	n	R^6	R^7	R^8
I-101	H	H	Cl	1	COSEt	Me	Me
I-102	H	H	Cl	1	CSSMe	Me	Me
I-103	Cl	H	Cl	2	COSEt	Me	Me
I-104	Cl	H	Cl	2	CSSMe	Me	Me

[Table 7]



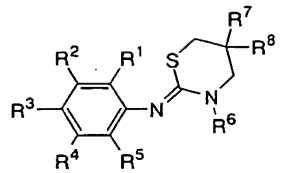
	R^6	W
I-109	COSEt	
I-116	CSSMe	
I-117	CSSMe	

[Table 8]



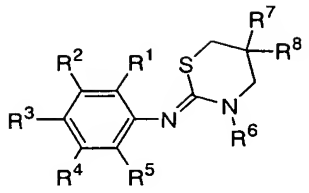
	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
I-124	H	H	OEt	H	H	CSSMe	Me	Me
I-125	H	OEt	H	H	H	CSSMe	Me	Me
I-126	H	H	OMe	H	H	CSSMe	Me	Me
I-127	H	OMe	H	H	H	CSSMe	Me	Me
I-128	H	OEt	OMe	H	H	CSSMe	Me	Me
I-129	H	OPr	OMe	H	H	CSSMe	Me	Me
I-130	H	OEt	OEt	H	H	CSSMe	Me	Me
I-131	H	H	OPr	H	H	CSSMe	Me	Me
I-132	H	OPr	H	H	H	CSSMe	Me	Me
I-133	H	H	OBu	H	H	CSSMe	Me	Me
I-134	H	OBu	H	H	H	CSSMe	Me	Me
I-135	H	OMe	OEt	H	H	CSSMe	Me	Me
I-136	H	OMe	OPr	H	H	CSSMe	Me	Me
I-137	H	OBu	OMe	H	H	CSSMe	Me	Me
I-138	H	H	OPr^i	H	H	CSSMe	Me	Me
I-139	H	OPr^i	H	H	H	CSSMe	Me	Me
I-140	H	H	H	H	H	CSSMe	Me	Me
I-141	F	H	H	H	H	CSSMe	Me	Me
I-142	Cl	H	H	H	H	CSSMe	Me	Me
I-143	H	Cl	H	H	H	CSSMe	Me	Me
I-144	Me	H	H	H	H	CSSMe	Me	Me
I-145	H	Me	H	H	H	CSSMe	Me	Me
I-146	H	H	Me	H	H	CSSMe	Me	Me
I-147	H	Bu	H	H	H	CSSMe	Me	Me
I-148	H	H	Bu	H	H	CSSMe	Me	Me
I-149	Bu^t	H	H	H	H	CSSMe	Me	Me
I-150	H	H	Et	H	H	CSSMe	Me	Me
I-151	H	Et	H	H	H	CSSMe	Me	Me
I-152	H	H	F	H	H	CSSMe	Me	Me
I-153	H	F	H	H	H	CSSMe	Me	Me
I-154	H	H	Pr^i	H	H	CSSMe	Me	Me
I-155	H	H	Morpholino	H	H	CSSMe	Me	Me
I-156	H	Ac	H	H	H	CSSMe	Me	Me
I-157	H	H	Br	H	H	CSSMe	Me	Me
I-158	H	Br	H	H	H	CSSMe	Me	Me
I-159	Br	H	H	H	H	CSSMe	Me	Me
I-160	H	C(Me)=NOMe	H	H	H	CSSMe	Me	Me
I-161	H	H	Ac	H	H	CSSMe	Me	Me
I-162	H	H	C(Me)=NOMe	H	H	CSSMe	Me	Me
I-163	OPr^i	H	H	H	H	CSSMe	Me	Me
I-164	Pr	H	H	H	H	CSSMe	Me	Me
I-165	CF_3	H	H	H	H	CSSMe	Me	Me

[Table 9]



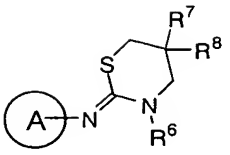
	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
I-166	H	H	OPh	H	H	CSSMe	Me	Me
I-167	H	H	Pr	H	H	CSSMe	Me	Me
I-168	H	H	Bu^t	H	H	CSSMe	Me	Me
I-169	H	CF_3	H	H	H	CSSMe	Me	Me
I-170	H	H	CF_3	H	H	CSSMe	Me	Me
I-171	Pr^i	H	NHAc	H	H	CSSMe	Me	Me
I-172	Pr^i	H	H	H	NHAc	CSSMe	Me	Me
I-173	H	COOMe	H	H	OMe	CSSMe	Me	Me
I-174	Morpholino	H	H	H	H	CSSMe	Me	Me
I-175	H	Morpholino	H	H	H	CSSMe	Me	Me
I-176	Pr^i	H	H	COO Et	H	CSSMe	Me	Me
I-177	H	H	Piperidino	H	H	CSSMe	Me	Me
I-178	Pyrrolidino	H	H	H	H	CSSMe	Me	Me
I-179	H	SMe	H	H	H	CSSMe	Me	Me
I-180	H	H	SMe	H	H	CSSMe	Me	Me
I-181	OCF_3	H	H	H	H	CSSMe	Me	Me
I-182	H	OCF_3	H	H	H	CSSMe	Me	Me
I-183	H	H	OCF_3	H	H	CSSMe	Me	Me
I-184	H	H	3-Pyridyl	H	H	CSSMe	Me	Me
I-185	H	3-Pyridyl	H	H	H	CSSMe	Me	Me
I-186	3-Pyridyl	H	H	H	H	CSSMe	Me	Me
I-187	OPh	H	H	H	H	CSSMe	Me	Me
I-188	H	OEt	OEt	H	H	COOMe	Me	Me
I-189	OMe	H	H	H	H	COOMe	Me	Me
I-190	H	H	Et	H	H	COOMe	Me	Me
I-191	H	H	Pr^i	H	H	COOMe	Me	Me
I-192	OMe	H	H	H	H	COSMe	Me	Me
I-193	H	H	Et	H	H	COSMe	Me	Me
I-194	H	H	Pr^i	H	H	COSMe	Me	Me
I-195	H	H	OEt	H	H	COSMe	Me	Me
I-196	H	OMe	OEt	H	H	COSMe	Me	Me
I-197	H	Piperidino	H	H	H	CSSMe	Me	Me
I-198	H	H	NEt_2	H	H	CSSMe	Me	Me
I-199	OMe	H	COOMe	H	H	CSSMe	Me	Me
I-200	H	2-Oxo pyrrolidino	H	H	H	CSSMe	Me	Me
I-201	H	OPh	H	H	H	CSSMe	Me	Me
I-202	H	H	Ph	H	H	CSSMe	Me	Me
I-203	Ph	H	H	H	H	CSSMe	Me	Me
I-204	H	Ph	H	H	H	CSSMe	Me	Me
I-205	Pr^i	H	H	H	H	CSOMe	Me	Me
I-206	Pr^i	H	I	H	H	CSSMe	Me	Me
I-207	OMe	H	(Morpholino)CO	H	H	CSSMe	Me	Me

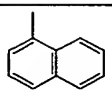
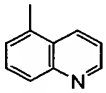
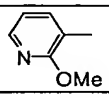
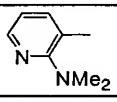
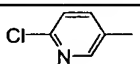
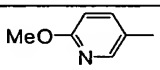
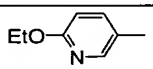
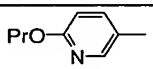
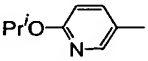
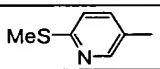
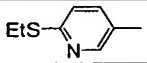
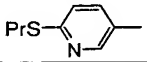
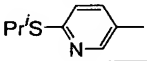
[Table 10]



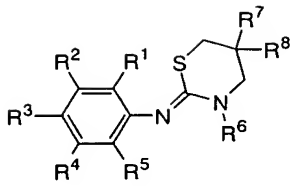
	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
I-208	H	H	NMe_2	H	H	CSSMe	Me	Me
I-209	H	NMe_2	H	H	H	CSSMe	Me	Me
I-210	N(Me)Et	H	H	H	H	CSSMe	Me	Me
I-211	N(Me)Pr	H	H	H	H	CSSMe	Me	Me
I-212	NEt_2	H	H	H	H	CSSMe	Me	Me
I-213	F	H	H	H	F	CSSMe	Me	Me
I-214	Pr^i	H	Cl	H	H	CSSMe	Me	Me
I-215	NMe_2	Me	H	H	H	CSSMe	Me	Me
I-216	NMe_2	H	Me	H	H	CSSMe	Me	Me
I-217	NMe_2	H	H	Me	H	CSSMe	Me	Me
I-218	NMe_2	H	H	Cl	H	CSSMe	Me	Me
I-219	Me	H	H	H	Me	CSSMe	Me	Me
I-220	NMe_2	H	H	H	H	CSSEt	Me	Me
I-221	H	NMe_2	H	H	H	CSSEt	Me	Me
I-222	NMe_2	H	Me	H	H	CSSEt	Me	Me
I-223	H	H	Pr^i	H	H	CSSEt	Me	Me
I-224	OMe	H	CONHMe	H	H	CSSMe	Me	Me
I-225	$OCHF_2$	H	H	H	H	CSSMe	Me	Me
I-226	H	$OCHF_2$	H	H	H	CSSMe	Me	Me
I-227	H	NEt_2	H	H	H	CSSMe	Me	Me
I-228	NMe_2	H	Cl	H	H	CSSMe	Me	Me
I-229	NMe_2	H	F	H	H	CSSMe	Me	Me
I-230	NMe_2	H	H	F	H	CSSMe	Me	Me
I-231	NMe_2	H	Et	H	H	CSSMe	Me	Me
I-232	NMe_2	H	H	Et	H	CSSMe	Me	Me
I-233	NMe_2	H	Cl	H	H	CSSEt	Me	Me
I-234	NMe_2	H	F	H	H	CSSEt	Me	Me
I-235	NMe_2	H	Et	H	H	CSSEt	Me	Me
I-236	Pr^i	H	H	H	H	$CSSBu^s$	Me	Me
I-237	Pr^i	H	H	H	H	$CSSBu^i$	Me	Me
I-239	Me	NMe_2	H	H	H	CSSMe	Me	Me
I-240	NMe_2	OMe	H	H	H	CSSMe	Me	Me
I-241	H	NMe_2	Me	H	H	CSSMe	Me	Me
I-242	NMe_2	Cl	H	H	H	CSSMe	Me	Me
I-243	H	NMe_2	OMe	H	H	CSSMe	Me	Me
I-244	Pr^i	H	H	H	H	CSSEt	Et	Et

[Table 11]



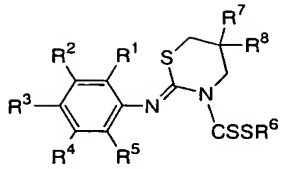
	A	R^6	R^7	R^8
I-249		CSSMe	Me	Me
I-250		CSSMe	Me	Me
I-251		CSSMe	Me	Me
I-252		CSSMe	Me	Me
I-253		CSSMe	Me	Me
I-254		CSSMe	Me	Me
I-255		CSSMe	Me	Me
I-256		CSSMe	Me	Me
I-257		CSSMe	Me	Me
I-258		CSSMe	Me	Me
I-259		CSSMe	Me	Me
I-260		CSSMe	Me	Me
I-261		CSSMe	Me	Me

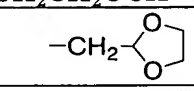
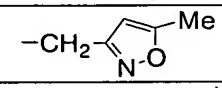
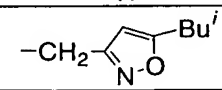
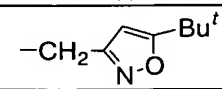
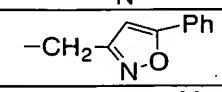
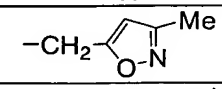
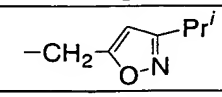
[Table 12]



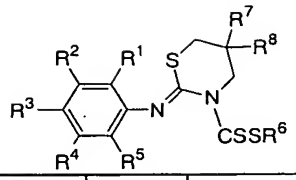
	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
I-262	NMe_2	H	OMe	H	H	CSSMe	Me	Me
I-263	NMe_2	H	H	OMe	H	CSSMe	Me	Me
I-264	Me	NEt_2	H	H	H	CSSMe	Me	Me
I-265	H	NEt_2	Me	H	H	CSSMe	Me	Me
I-266	H	NEt_2	OMe	H	H	CSSMe	Me	Me
I-267	Bu^s	H	H	H	H	CSSMe	Et	Et
I-268	Pr^i	H	H	H	H	CSSMe	Pr	Pr
I-269	Pr^i	H	H	H	H	CSSMe	$-(CH_2)_4-$	
I-270	Pr^i	H	H	H	H	CSSMe	$-(CH_2)_5-$	

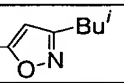
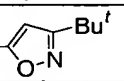
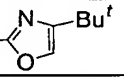
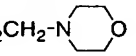
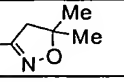
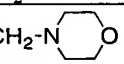
[Table 13]



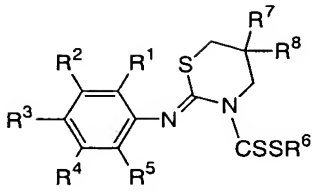
No	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
II-1	Pr^i	H	H	H	H	Allyl	Me	Me
II-2	Pr^i	H	H	H	H	Propargyl	Me	Me
II-3	Pr^i	H	H	H	H	CH_2CN	Me	Me
II-4	Pr^i	H	H	H	H	CH_2OMe	Me	Me
II-5	Pr^i	H	H	H	H	$CH_2CH=CHMe$	Me	Me
II-6	Pr^i	H	H	H	H	$CH_2CH=CMe_2$	Me	Me
II-7	Pr^i	H	H	H	H	$CH_2CH_2CH=CH_2$	Me	Me
II-8	Pr^i	H	H	H	H	CH_2COMe	Me	Me
II-9	Pr^i	H	H	H	H	CH_2CO_2H	Me	Me
II-10	Pr^i	H	H	H	H	CH_2CO_2Me	Me	Me
II-11	Pr^i	H	H	H	H	CH_2CO_2Et	Me	Me
II-12	Pr^i	H	H	H	H	CH_2CO_2Pr	Me	Me
II-13	Pr^i	H	H	H	H	$CH_2CO_2Pr^i$	Me	Me
II-14	Pr^i	H	H	H	H	$CH_2CO_2Bu^t$	Me	Me
II-15	Pr^i	H	H	H	H	$CH_2CO_2CH=CH_2$	Me	Me
II-16	Pr^i	H	H	H	H	$CH_2CO_2CH_2CH=CH_2$	Me	Me
II-17	Pr^i	H	H	H	H	$CH_2CO_2(CH_2)_2OMe$	Me	Me
II-18	Pr^i	H	H	H	H	$CH(Me)CO_2Me$	Me	Me
II-19	Pr^i	H	H	H	H	$C(Me)_2CO_2Et$	Me	Me
II-20	Pr^i	H	H	H	H	CH_2CONH_2	Me	Me
II-21	Pr^i	H	H	H	H	CH_2CONMe_2	Me	Me
II-22	Pr^i	H	H	H	H	$CH_2CON(Me)OMe$	Me	Me
II-23	Pr^i	H	H	H	H	CH_2CF_3	Me	Me
II-24	Pr^i	H	H	H	H	CH_2CH_2OCOMe	Me	Me
II-25	Pr^i	H	H	H	H	CH_2CH_2OPh	Me	Me
II-26	Pr^i	H	H	H	H	$CH_2CH_2OCH=CH_2$	Me	Me
II-27	Pr^i	H	H	H	H		Me	Me
II-28	Pr^i	H	H	H	H		Me	Me
II-29	Pr^i	H	H	H	H		Me	Me
II-30	Pr^i	H	H	H	H		Me	Me
II-31	Pr^i	H	H	H	H		Me	Me
II-32	Pr^i	H	H	H	H		Me	Me
II-33	Pr^i	H	H	H	H		Me	Me

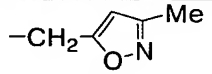
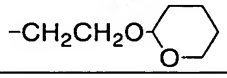
[Table 14]



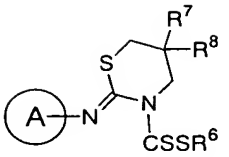
No	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
II-34	Pr^i	H	H	H	H		Me	Me
II-35	Pr^i	H	H	H	H		Me	Me
II-36	Pr^i	H	H	H	H		Me	Me
II-37	Pr^i	H	H	H	H		Me	Me
II-38	Pr^i	H	H	H	H		Me	Me
II-39	Pr^i	H	H	H	H	Allyl	Et	Et
II-40	Pr^i	H	H	H	H	CH_2CO_2Et	Et	Et
II-41	Pr^i	H	H	H	H	$CH_2CO_2Pr^i$	Et	Et
II-42	Pr^i	H	H	H	H	$CH_2CO_2Bu^t$	Et	Et
II-43	Pr^i	H	H	H	H	$CH_2CH_2CO_2Et$	Et	Et
II-44	Pr^i	H	H	H	H	$CH_2CH=CHMe$	Et	Et
II-45	Pr^i	H	H	H	H	$CH_2CH=CMe_2$	Et	Et
II-46	Pr^i	H	H	H	H	$CH_2CH_2CH=CH_2$	Et	Et
II-47	Bu^s	H	H	H	H	CH_2CO_2Et	Me	Me
II-48	Bu^s	H	H	H	H	$CH_2CO_2Bu^t$	Me	Me
II-49	Bu^s	H	H	H	H	Allyl	Et	Et
II-50	Bu^s	H	H	H	H	CH_2CH_2OCOMe	Et	Et
II-51	Bu^s	H	H	H	H		Et	Et
II-52	H	H	Et	H	H	CH_2CO_2Et	Me	Me
II-53	H	Pr^i	H	H	H	CH_2CO_2Et	Me	Me
II-54	NMe_2	H	H	H	H	CH_2CO_2Et	Me	Me
II-55	H	NMe_2	H	H	H	CH_2CO_2Et	Me	Me
II-56	H	NEt_2	H	H	H	CH_2CO_2Et	Me	Me
II-57	H	H	Et	H	H	$CH_2CO_2Bu^t$	Me	Me
II-58	H	Pr^i	H	H	H	$CH_2CO_2Bu^t$	Me	Me
II-59	NMe_2	H	H	H	H	$CH_2CO_2Bu^t$	Me	Me
II-60	H	NMe_2	H	H	H	$CH_2CO_2Bu^t$	Me	Me
II-61	H	NEt_2	H	H	H	$CH_2CO_2Bu^t$	Me	Me
II-62	H	NEt_2	H	H	H	Allyl	Me	Me
II-63	Me	NEt_2	H	H	H	Allyl	Me	Me
II-64	Me	NMe_2	H	H	H	Allyl	Me	Me
II-65	NMe_2	H	H	H	H	Allyl	Et	Et
II-66	NMe_2	H	H	H	H	$CH_2CO_2Bu^t$	Et	Et
II-67	OMe	H	H	H	H	Allyl	Et	Et
II-68	OMe	H	H	H	H	$CH_2CO_2Bu^t$	Et	Et
II-69	H	H	Et	H	H	Allyl	Et	Et

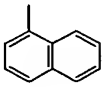
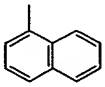
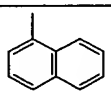
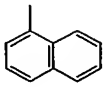
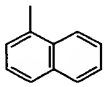
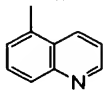
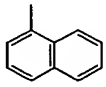
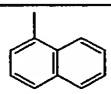
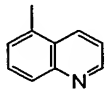
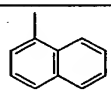
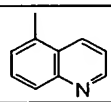
[Table 15]



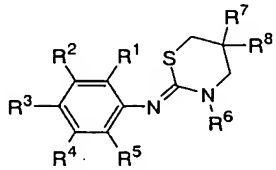
No	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
II-70	H	H	Et	H	H	$CH_2CO_2Bu^t$	Et	Et
II-71	H	H	OCF_3	H	H	Allyl	Et	Et
II-72	H	H	OCF_3	H	H	$CH_2CO_2Bu^t$	Et	Et
II-73	NMe_2	H	H	H	H	CH_2OMe	Et	Et
II-74	Pr^i	H	H	H	H	Allyl	$-(CH_2)_4-$	
II-75	NMe_2	H	H	H	H	Allyl	$-(CH_2)_4-$	
II-76	NMe_2	H	H	H	H	$CH_2CO_2Bu^t$	$-(CH_2)_4-$	
II-77	Pr^i	H	H	H	H	$CH_2CO_2(CH_2)_2OMe$	$-(CH_2)_4-$	
II-78	Pr^i	H	H	H	H		$-(CH_2)_4-$	
II-79	OMe	H	H	H	H	Allyl	$-(CH_2)_4-$	
II-80	OMe	H	H	H	H	$CH_2CO_2Bu^t$	$-(CH_2)_4-$	
II-81	NMe_2	H	H	H	H	CH_2OMe	$-(CH_2)_4-$	
II-82	H	H	Et	H	H	Allyl	$-(CH_2)_4-$	
II-83	H	H	OCF_3	H	H	Allyl	$-(CH_2)_4-$	
II-84	NMe_2	H	H	H	H	Allyl	$-(CH_2)_5-$	
II-85	NMe_2	H	H	H	H	$CH_2CO_2Bu^t$	$-(CH_2)_5-$	
II-86	OMe	H	H	H	H	Allyl	$-(CH_2)_5-$	
II-87	OMe	H	H	H	H	$CH_2CO_2Bu^t$	$-(CH_2)_5-$	
II-88	H	H	Et	H	H	Allyl	$-(CH_2)_5-$	
II-89	Pr^i	H	H	H	H		$-(CH_2)_5-$	
II-90	Pr^i	H	H	H	H	CH_2CH_2OH	$-(CH_2)_5-$	
II-91	H	H	OCF_3	H	H	Allyl	$-(CH_2)_5-$	
II-92	Pr^i	H	H	H	H	Allyl	$-(CH_2)_2O(CH_2)_2-$	
II-93	Pr^i	H	H	H	H	Me	$-(CH_2)_2O(CH_2)_2-$	
II-94	Pr^i	H	H	H	H	CH_2CO_2H	Et	Et

[Table 16]



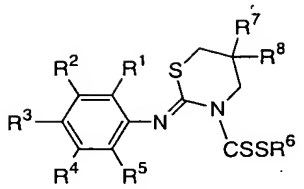
	A	R^6	R^7	R^8
II-95		Allyl	Me	Me
II-96		$CH_2CO_2Bu^t$	Me	Me
II-97		$CH_2CO_2(CH_2)_2OMe$	Me	Me
II-98		Allyl	Et	Et
II-99		$CH_2CO_2Bu^t$	Et	Et
II-100		Allyl	Et	Et
II-101		Allyl	$-(CH_2)_4-$	
II-102		$CH_2CO_2Bu^t$	$-(CH_2)_4-$	
II-103		Allyl	$-(CH_2)_4-$	
II-104		Allyl	$-(CH_2)_5-$	
II-105		Allyl	$-(CH_2)_5-$	

[Table 17]



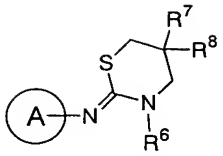
	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
II-113	Pr^i	H	H	H	H	CSSMe	$-(CH_2)_2N(CH_2Ph)(CH_2)_2-$	

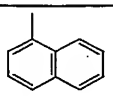
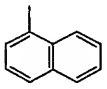
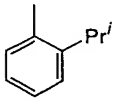
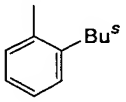
[Table 18]



	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
II-114	H	SMe	H	H	H	Allyl	Et	Et
II-115	H	SMe	H	H	H	Allyl	$-(CH_2)_4-$	
II-116	H	SMe	H	H	H	Allyl	$-(CH_2)_5-$	
II-117	H	H	SMe	H	H	Allyl	$-(CH_2)_4-$	
II-118	H	H	SMe	H	H	Allyl	$-(CH_2)_5-$	
II-119	OMe	H	Et	H	H	Allyl	Me	Me
II-120	OMe	H	Pr^i	H	H	Allyl	Me	Me
II-121	Pr^i	H	OMe	H	H	Allyl	Me	Me
II-122	Pr^i	H	OEt	H	H	Allyl	Me	Me
II-123	H	OEt	OEt	H	H	Allyl	Me	Me
II-124	H	OPr	OPr	H	H	Allyl	Me	Me
II-125	H	OMs	OEt	H	H	Allyl	Me	Me
II-126	H	H	$(CH_2)_2OEt$	H	H	Allyl	Me	Me
II-127	H	OMe	OEt	H	H	Allyl	Et	Et
II-128	H	OEt	OEt	H	H	Allyl	Et	Et
II-129	H	OEt	OPr	H	H	Allyl	Et	Et
II-130	H	OMs	OPr	H	H	Allyl	Et	Et
II-131	H	OPr	OPr	H	H	Allyl	Et	Et
II-132	H	OPr^i	OPr	H	H	Allyl	Et	Et
II-133	H	H	$(CH_2)_2NMe_2$	H	H	Allyl	Me	Me
II-134	Pr^i	H	H	H	H	$CH_2CO_2Bu^t$	$-(CH_2)_5-$	
II-135	Pr^i	H	H	H	H	Me	$-(CH_2)_2N(Me)(CH_2)_2-$	
II-136	Pr^i	H	H	H	H	Me	$-(CH_2)_2N(Et)(CH_2)_2-$	
II-137	F	H	F	H	H	Allyl	Me	Me
II-138	H	Cl	Cl	H	H	Allyl	Me	Me
II-139	Me	H	Cl	H	H	Allyl	Me	Me
II-140	Cl	H	Me	H	H	Allyl	Me	Me
II-141	H	H	$(CH_2)_2OMe$	H	H	Allyl	Me	Me
II-142	H	H	Pr^i	H	H	Allyl	$-(CH_2)_4-$	
II-143	H	H	Pr^i	H	H	$CH_2CO_2Bu^t$	$-(CH_2)_4-$	
II-144	H	H	Pr^i	H	H	Allyl	Et	Et
II-145	H	H	Pr^i	H	H	$CH_2CO_2Bu^t$	Et	Et
II-146	H	H	Pr^i	H	H	Allyl	$-(CH_2)_5-$	
II-147	OMe	H	H	H	H	$CH_2CO_2Bu^t$	Pr	Pr
II-148	OMe	H	H	H	H	$CH_2CO_2Bu^t$	Pr^i	Pr^i
II-149	OMe	H	H	H	H	Allyl	Pr	Pr
II-150	Bu^s	H	H	H	H	Me	$-(CH_2)_2N(Me)(CH_2)_2-$	

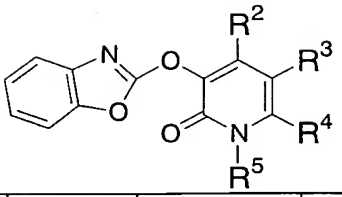
[Table 19]

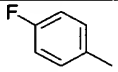
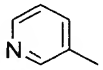
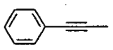


	A	R^6	R^7	R^8
II-151		$CSSCH_2CO_2Bu^t$	$-(CH_2)_5-$	
II-152		$CSSCH_2CO_2Bu^t$	Et	Et
II-153		COSMe	$-(CH_2)_2N(Me)(CH_2)_2-$	
II-154		COSMe	$-(CH_2)_2N(Me)(CH_2)_2-$	

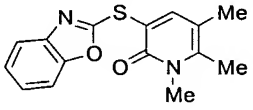
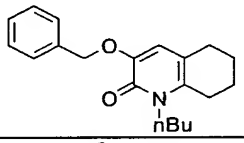
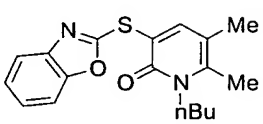
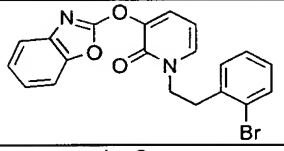
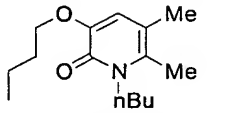
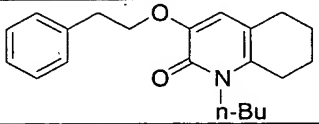
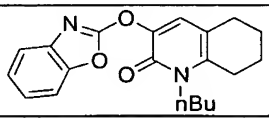
The compounds described in WO 02/053543 are exemplified as the compound represented by the formula (II). Preferable are the compounds described in the following Tables.

[Table 20]

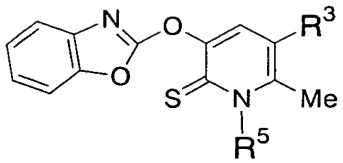


Compoud No.	R^2	R^3	R^4	R^5
1-001	H	Me	Me	Me
1-002	H	Me	Me	Et
1-003	H	Me	Me	nPr
1-004	H	Me	Me	nBu
1-005	H	Me	Me	Bn
1-006	H		H	nBu
1-007	H		H	nBu
1-008	H		H	nBu
1-009	H		H	nBu
1-010	Me	H	Me	nBu
1-011		H	Me	nBu

[Table 21]

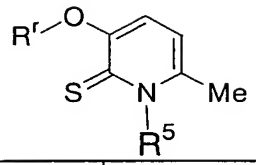
Compound No.	Structure	Compound No.	Structure
1-012		1-016	
1-013		1-017	
1-014		1-019	
1-015			

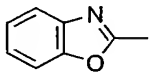
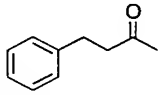
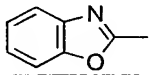
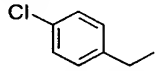
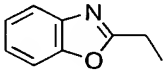
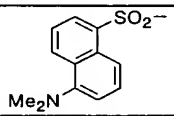
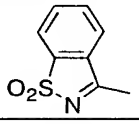
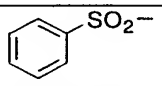
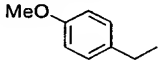
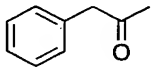
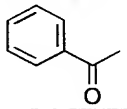
[Table 22]



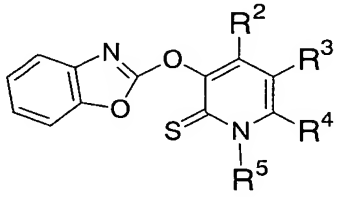
Compound No.	R^3	R^5	Compound No.	R^3	R^5
2-001	Me	Me	2-008	Me	Bn
2-002	Me	Et	2-009	Et	Me
2-003	Me	nPr	2-010	Et	Et
2-004	Me	nBu	2-011	Et	nPr
2-005	Me	iBu	2-012	Et	nBu
2-006	Me	nPent	2-013	Et	Bn
2-007	Me	nHexyl			

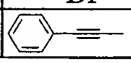
[Table 23]



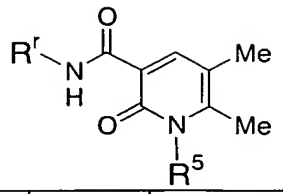
Compound No.	R^r	R^5	Compound No.	R^r	R^5
2-014		Me	2-022		nBu
2-015		nBu	2-023		nBu
2-016		nBu	2-024		nBu
2-017	Ac	nBu	2-025		nBu
2-018	H	nBu	2-026	nBu	nBu
2-019		nBu	2-027		nBu
2-020	H_3C-SO_2-	nBu	2-028	EtO_2C-	nBu
2-021		nBu	2-029		nBu

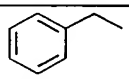
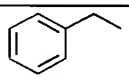
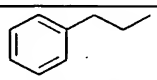
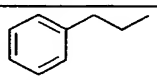
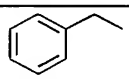
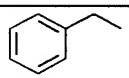
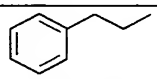
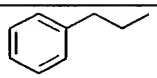
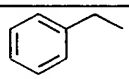
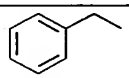
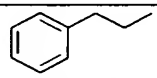
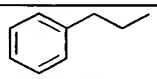
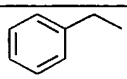
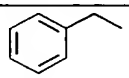
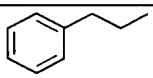
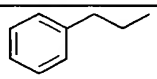
[Table 24]



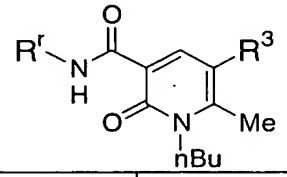
Compoud No.	R^2	R^3	R^4	R^5
2-030	H	H	H	iPr
2-031	Me	H	H	nPr
2-032	-CH_2OMe	H	H	nPr
2-033	H	H	H	nBu
2-034	Me	H	H	nBu
2-035	H	Me	H	nBu
2-036	H	Br	H	nBu
2-037	H		H	nBu

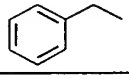
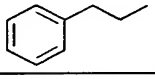
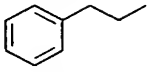
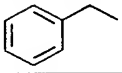
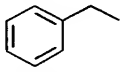
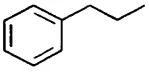
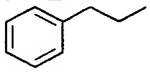
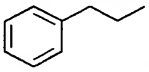
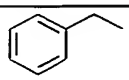
[Table 25]



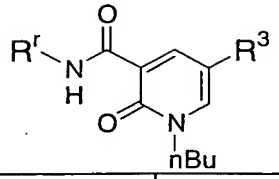
Compound No..	R^r	R^5	Compound No..	R^r	R^5
3-001		Me	3-009		nBu
3-002		Me	3-010		nBu
3-003		Et	3-011		nHexyl
3-004		Et	3-012		nHexyl
3-005		nPr	3-013		Bn
3-006		nPr	3-014		Bn
3-007		iPr	3-015		Ph
3-008		iPr	3-016		Ph

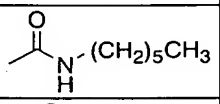
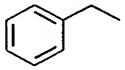
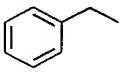
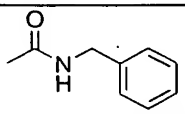
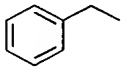
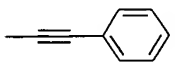
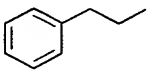
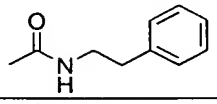
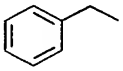
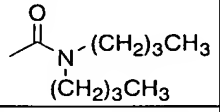
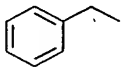
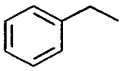
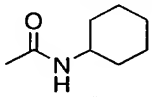
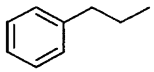
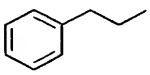
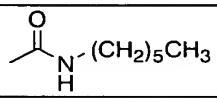
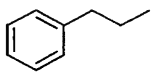
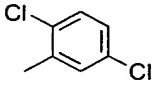
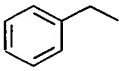
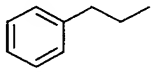
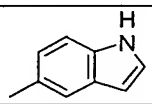
[Table 26]



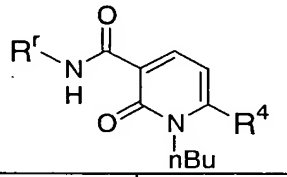
Compound No..	R^r	R^3	Compound No..	R^r	R^3
3-033		nBu	3-038		I
3-034		nBu	3-039		
3-035		nPentyl	3-040		
3-036		nPentyl	3-044		CF_3
3-037		I			

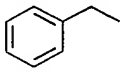
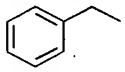
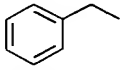
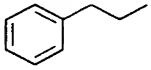
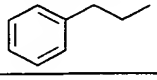
[Table 27]



Compound No..	R^r	R^3	Compound No.	R^r	R^3
3-061	n-Hexyl		3-068		
3-062			3-069		
3-063			3-070	nBuO	H
3-064			3-071		H
3-065			3-072		CF_3
3-066			3-073		
3-067		I	3-074		

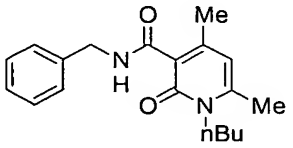
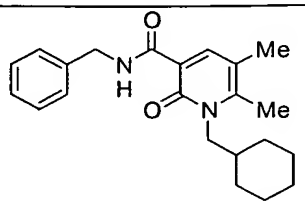
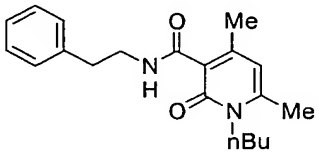
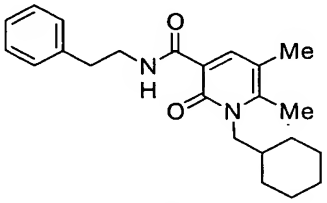
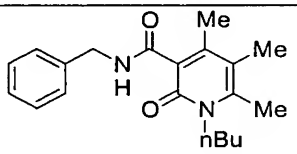
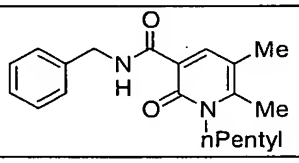
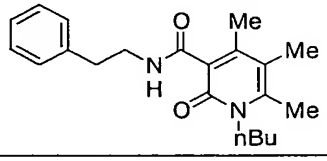
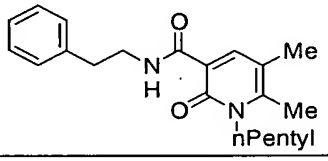
[Table 28]



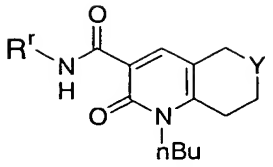
Compound No..	R^r	R^4	Compound No..	R^r	R^4
3-081		Me	3-084		nHexyl
3-082		nPentyl	3-085		nHexyl
3-083		nPentyl			

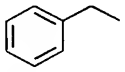
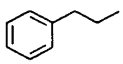
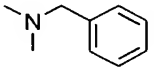
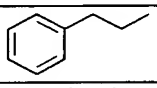
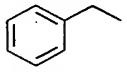
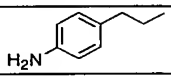
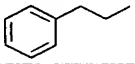
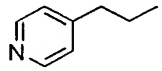
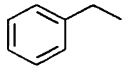
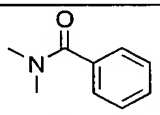
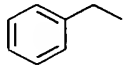
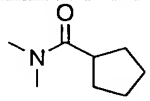
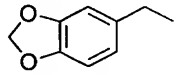
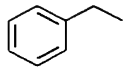
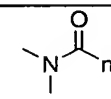
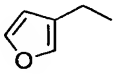
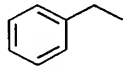
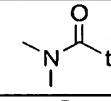
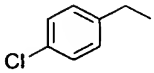
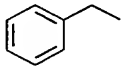
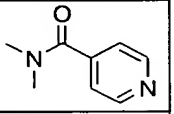
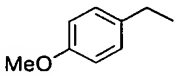
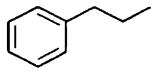
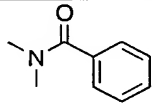
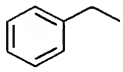
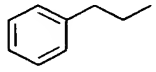
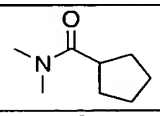
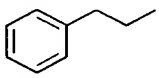
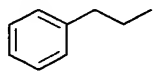
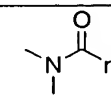
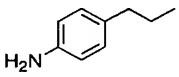
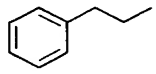
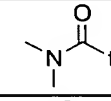
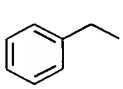
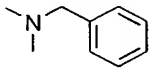
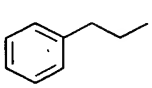
5

[Table 29]

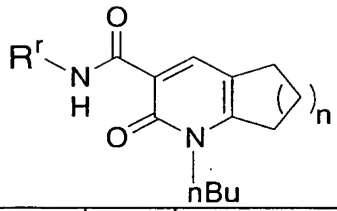
Compound No..	Structure	Compound No..	Structure
3-105		3-109	
3-106		3-110	
3-107		3-111	
3-108		3-112	

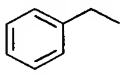
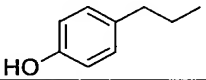
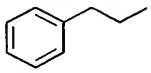
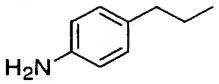
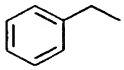
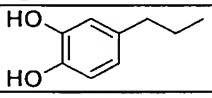
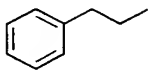
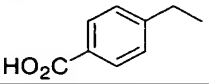
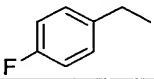
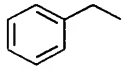
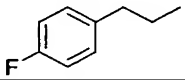
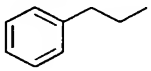
[Table 30]



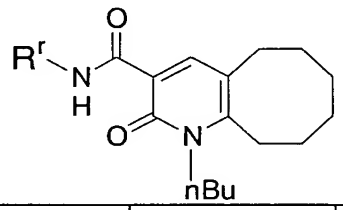
Compound No.	R^r	Y	Compound No.	R^r	Y
4-001		$-CH_2-$	4-014		
4-002		$-CH_2-$	4-015		
4-003		$-CH_2-$	4-016		
4-004		$-CH_2-$	4-017		
4-005		$-CH_2-$	4-018		
4-006		$-CH_2-$	4-019		
4-007		$-CH_2-$	4-020		
4-008		$-CH_2-$	4-021		
4-009		$-CH_2-$	4-022		
4-010		-O-	4-023		
4-011		-O-	4-024		
4-012		-O-	4-025		
4-013			4-026		

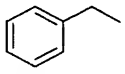
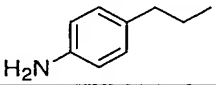
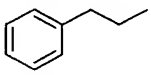
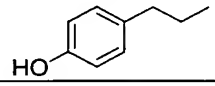
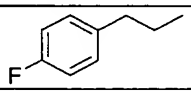
[Table 31]



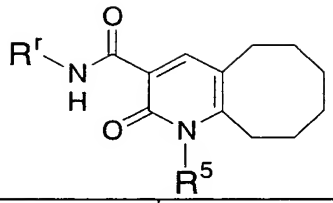
Compound No.	R^r	n	Compound No.	R^r	n
4-051		1	4-057		3
4-052		1	4-058		3
4-053		3	4-059		3
4-054		3	4-060		3
4-055		3	4-061		6
4-056		3	4-062		6

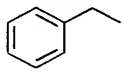
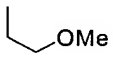
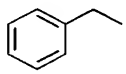
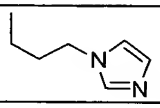
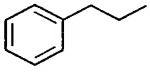
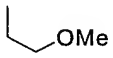
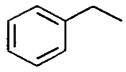
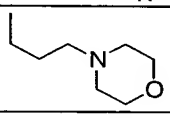
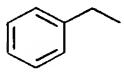
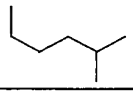
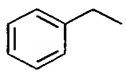
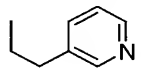
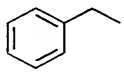
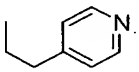
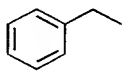
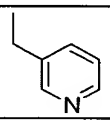
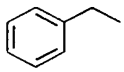
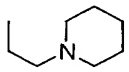
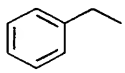
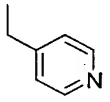
[Table 32]



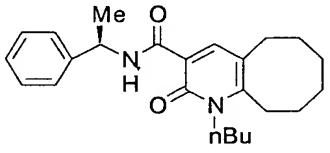
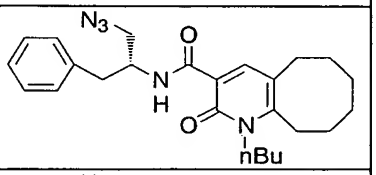
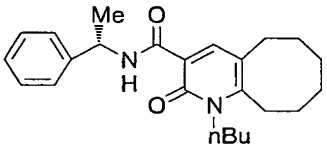
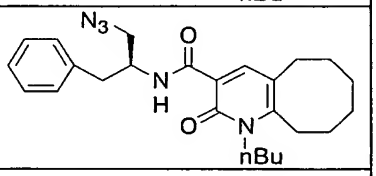
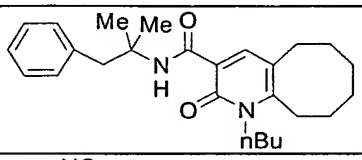
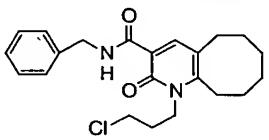
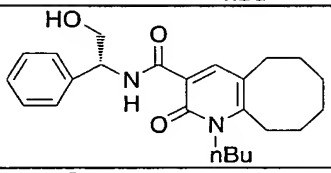
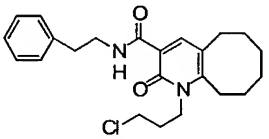
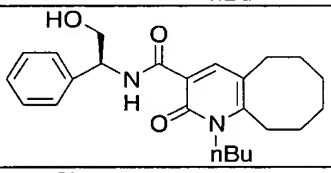
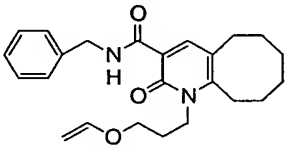
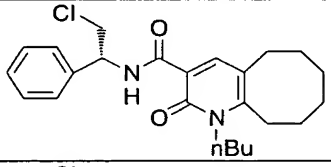
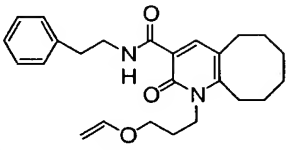
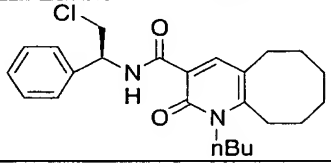
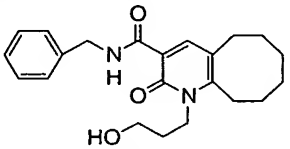
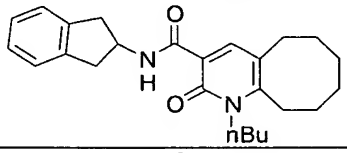
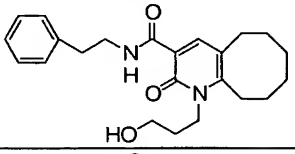
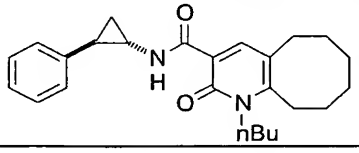
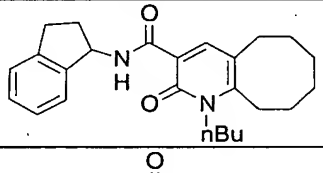
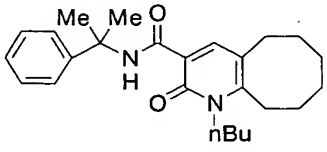
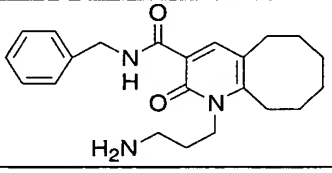
Compound No.	R^r	Compound No.	R^r
4-101		4-104	
4-102		4-105	
4-103			

[Table 33]

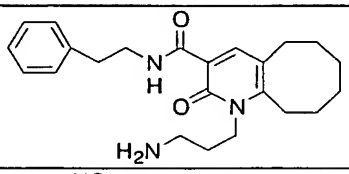
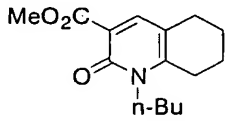
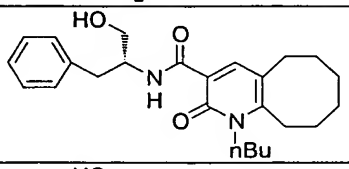
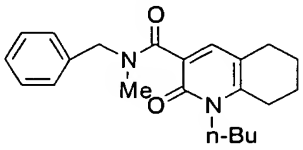
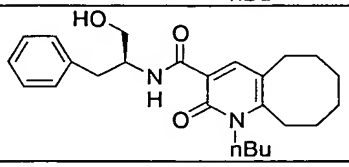


Compound No.	R^r	R^5	Compound No.	R^r	R^5
4-301			4-306		
4-302			4-307		
4-303			4-308		
4-304			4-309		
4-305			4-310		

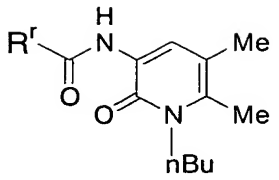
[Table 34]

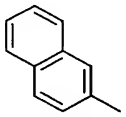
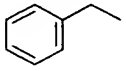
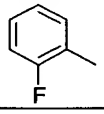
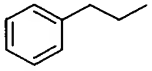
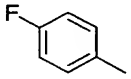
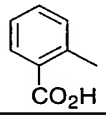
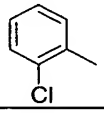
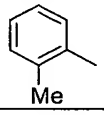
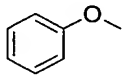
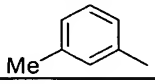
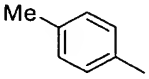
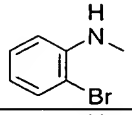
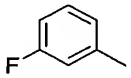
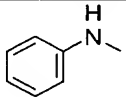
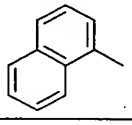
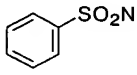
Compound No.	Structure	Compound No.	Structure
4-311		4-321	
4-312		4-322	
4-313		4-323	
4-314		4-324	
4-315		4-325	
4-316		4-326	
4-317		4-327	
4-318		4-328	
4-319		4-329	
4-320		4-330	

[Table 35]

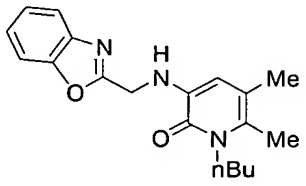
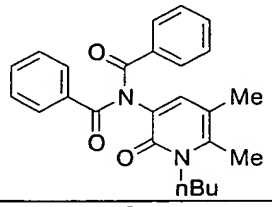
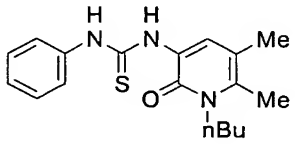
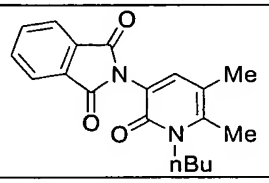
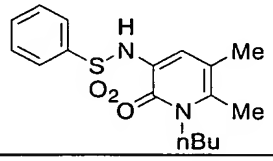
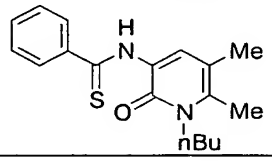
Compound No.	Structure	Compound No.	Structure
4-331		4-505	
4-332		4-506	
4-333			

[Table 36]

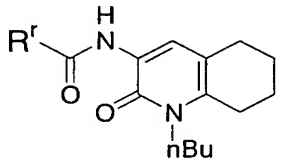


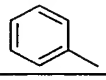
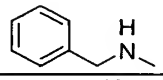
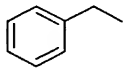
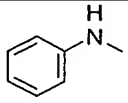
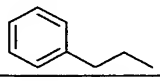
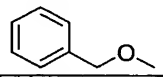
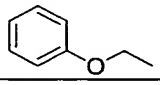
Compound No.	R^r	Compound No.	R^r
5-001	Me	5-011	
5-002		5-012	
5-003		5-013	
5-004		5-014	
5-005		5-015	nBuO-
5-006		5-016	
5-007		5-017	BnO-
5-008		5-018	
5-009		5-019	
5-010		5-020	

[Table 37]

Compound No.	Structure	Compound No.	Structure
5-101		5-104	
5-102		5-105	
5-103		5-106	

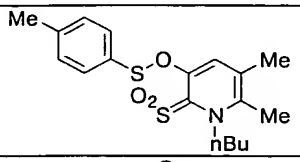
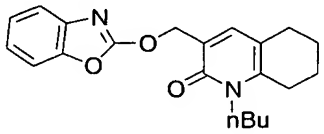
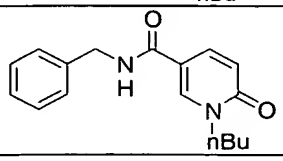
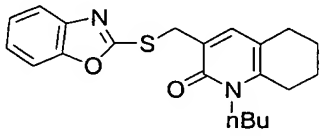
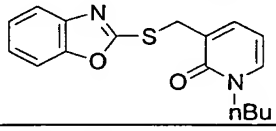
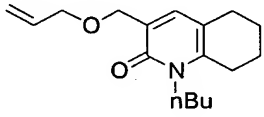
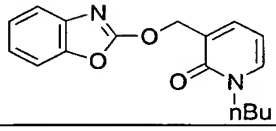
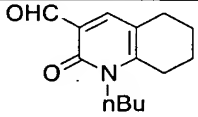
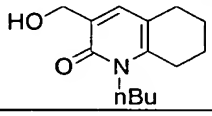
[Table 38]



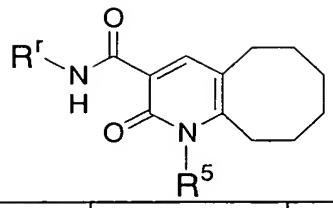
Compound No.	R^r	Compound No.	R^r
6-001		6-005	
6-002		6-006	
6-003		6-007	
6-004			

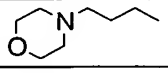
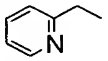
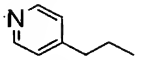
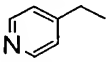
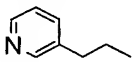
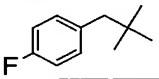
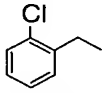
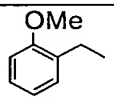
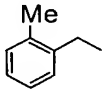
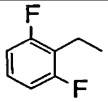
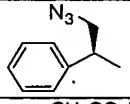
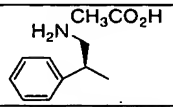
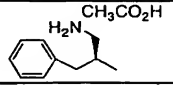
5

[Table 39]

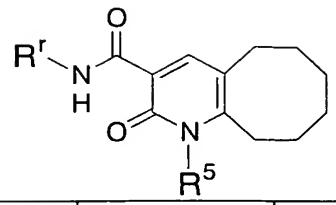
Compound No.	Structure	Compound No.	Structure
7-002		7-020	
7-007		7-021	
7-008		7-022	
7-009		7-023	
7-019			

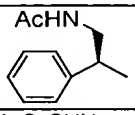
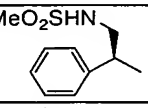
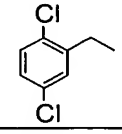
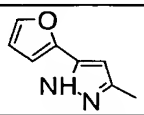
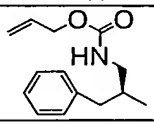
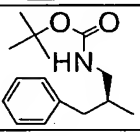
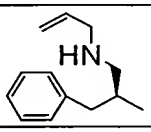
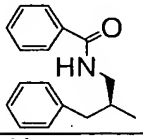
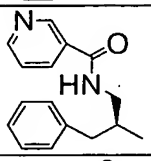
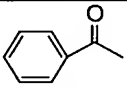
[Table 40]



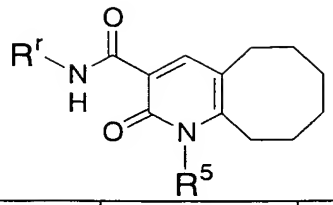
Compound No.	R^r	R^5
10-001		nBu
10-002		nBu
10-003		nBu
10-004		nBu
10-005		nBu
10-006		nBu
10-007		nBu
10-008		nBu
10-009		nBu
10-010		nBu
10-011		nBu
10-012		nBu
10-013		nBu

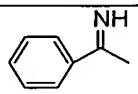
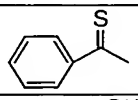
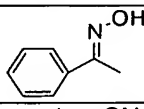
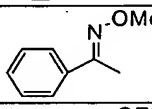
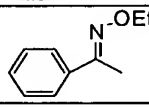
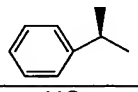
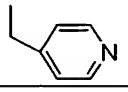
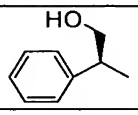
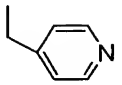
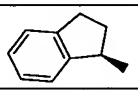
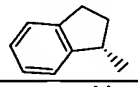
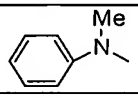
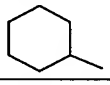
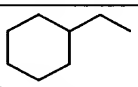
[Table 41]



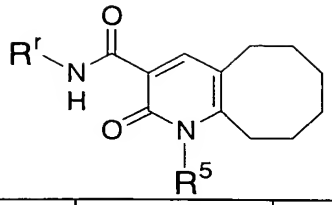
Compound No.	R^r	R^5
10-014		nBu
10-015		nBu
10-016		nBu
10-017		nBu
10-018		nBu
10-019		nBu
10-020		nBu
10-021		nBu
10-022		nBu
10-023		nBu
10-024	H-	nBu

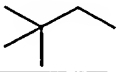
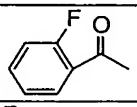
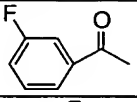
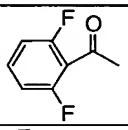
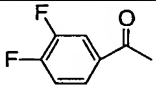
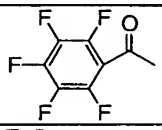
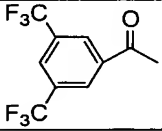
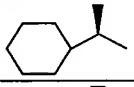
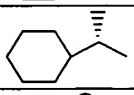
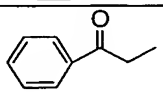
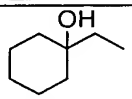
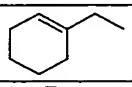
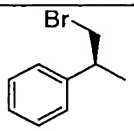
[Table 42]



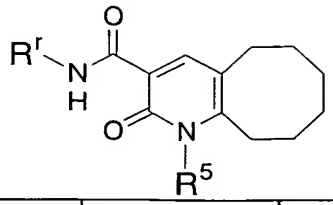
Compound No.	R^r	R^5
10-025		nBu
10-026		nBu
10-027		nBu
10-028		nBu
10-029		nBu
10-030		
10-031		
10-032		nBu
10-033		nBu
10-034		nBu
10-035		nBu
10-036		nBu
10-037	Me	nBu
10-038	Et	nBu
10-039	iPr	nBu
10-040	tBu	nBu

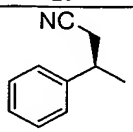
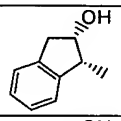
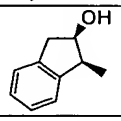
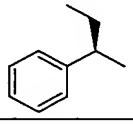
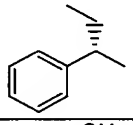
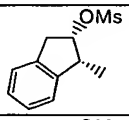
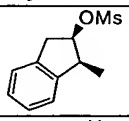
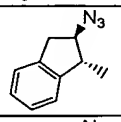
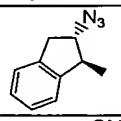
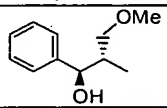
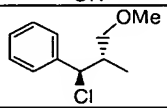
[Table 43]



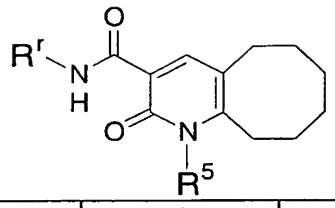
Compound No.	R^r	R^5
10-041		nBu
10-042		nBu
10-043		nBu
10-045		nBu
10-046		nBu
10-047		nBu
10-048		nBu
10-049		nBu
10-050		nBu
10-051		nBu
10-052		nBu
10-053		nBu
10-054		nBu

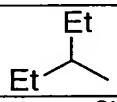
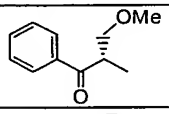
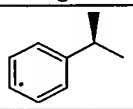
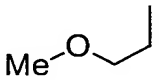
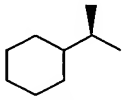
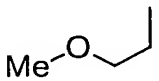
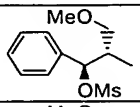
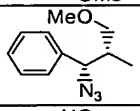
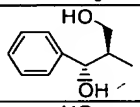
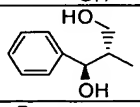
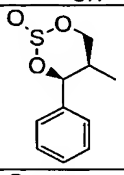
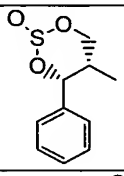
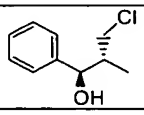
[Table 44]



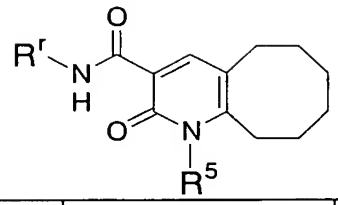
Compound No.	R^r	R^5
10-055		nBu
10-056		nBu
10-057		nBu
10-058		nBu
10-059		nBu
10-060		nBu
10-061		nBu
10-062		nBu
10-063		nBu
10-064		nBu
10-065		Bu

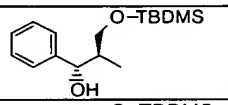
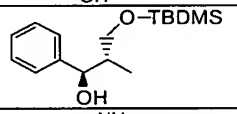
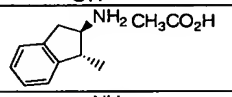
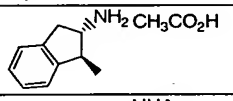
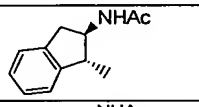
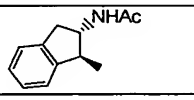
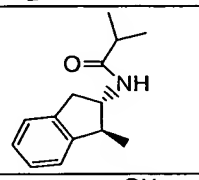
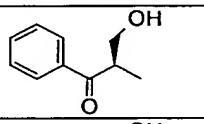
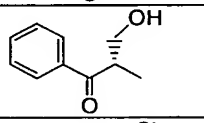
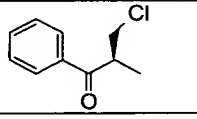
[Table 45]



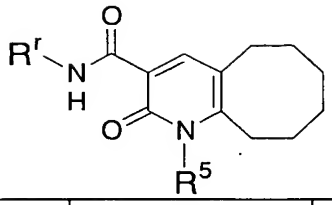
Compound No.	R^r	R^5
10-066		Bu
10-067		Bu
10-068		
10-069		
10-070		nBu
10-071		nBu
10-072		nBu
10-073		nBu
10-074		nBu
10-075		nBu
10-076		nBu

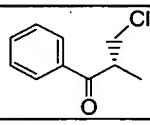
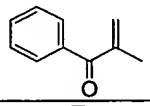
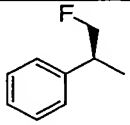
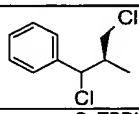
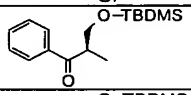
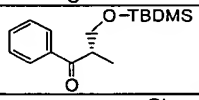
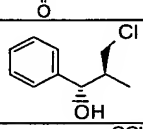
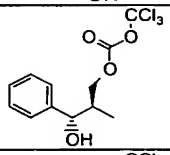
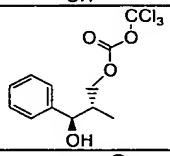
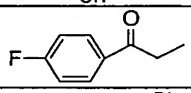
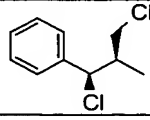
[Table 46]



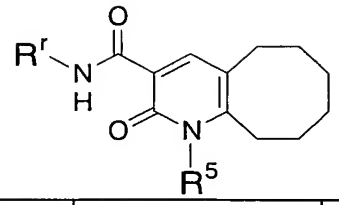
Compound No.	R^r	R^5
10-077		nBu
10-078		nBu
10-079		nBu
10-080		nBu
10-081		nBu
10-082		nBu
10-083		nBu
10-084		nBu
10-085		nBu
10-086		nBu

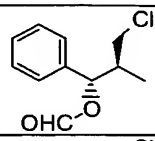
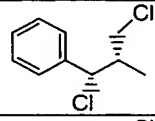
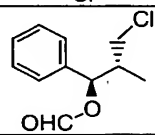
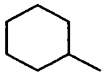
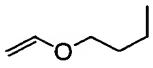
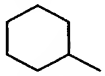
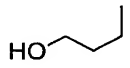
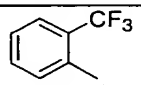
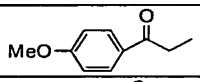
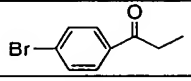
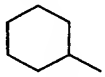
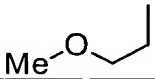
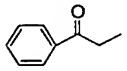
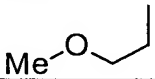
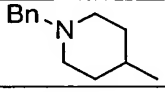
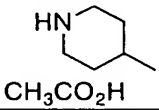
[Table 47]



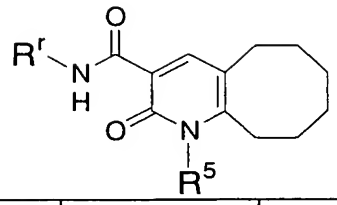
Compound No.	R^r	R^5
10-087		nBu
10-088		nBu
10-089		nBu
10-090		nBu
10-091		nBu
10-092		nBu
10-093		nBu
10-094		nBu
10-095		nBu
10-096		nBu
10-097		nBu

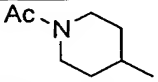
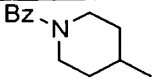
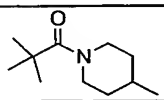
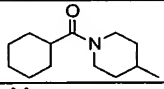
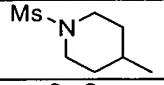
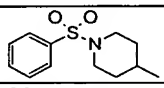
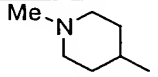
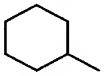
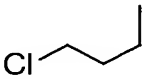
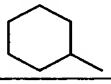
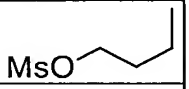
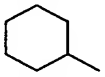
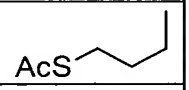
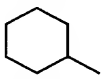
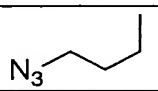
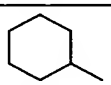
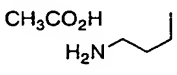
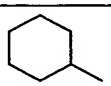
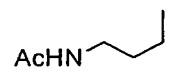
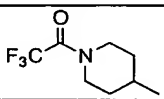
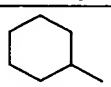
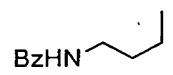
[Table 48]



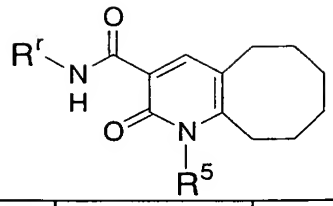
Compound No.	R^r	R^5
10-098		nBu
10-099		nBu
10-100		nBu
10-101		
10-102		
10-103		nBu
10-104		nBu
10-105		nBu
10-106		
10-107		
10-108		nBu
10-109		nBu

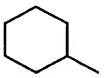
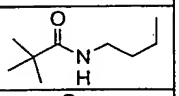
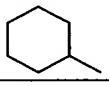
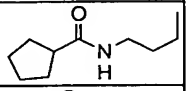
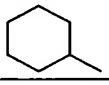
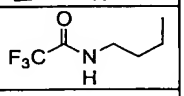
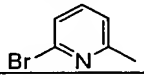
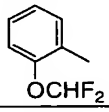
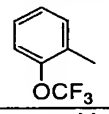
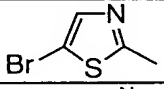
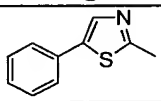
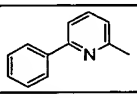
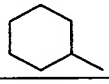
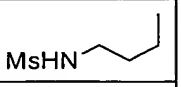
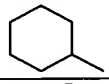
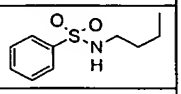
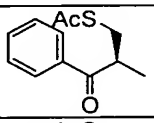
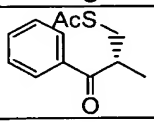
[Table 49]



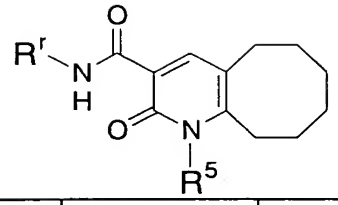
Compound No.	R^r	R^5
10-110		nBu
10-111		nBu
10-112		nBu
10-113		nBu
10-114		nBu
10-115		nBu
10-116		nBu
10-117		
10-118		
10-119		
10-120		
10-121		
10-122		
10-123		nBu
10-124		

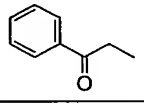
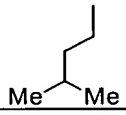
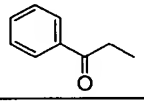
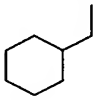
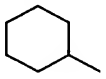
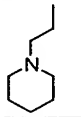
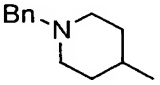
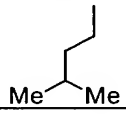
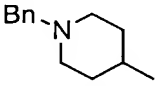
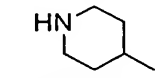
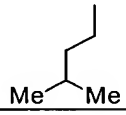
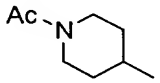
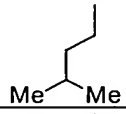
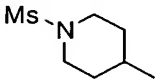
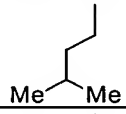
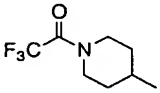
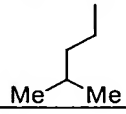
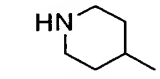
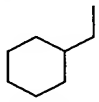
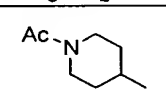
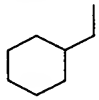
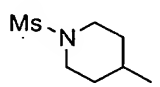
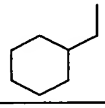
[Table 50]



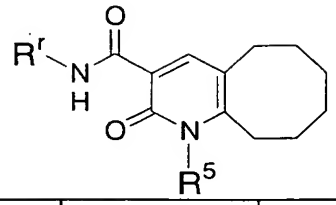
Compound No.	R^r	R^5
10-125		
10-126		
10-127		
10-128		nBu
10-129		nBu
10-130		nBu
10-131		nBu
10-132		nBu
10-133		nBu
10-134		
10-135		
10-136		nBu
10-137		nBu

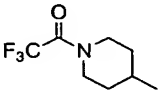
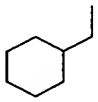
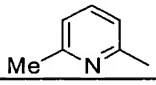
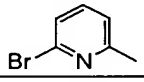
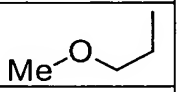
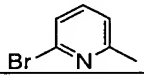
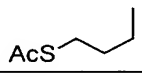
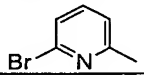
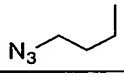
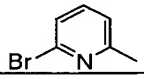
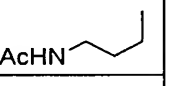
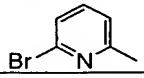
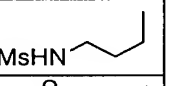
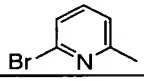
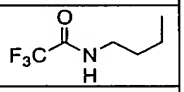
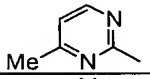
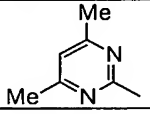
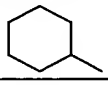
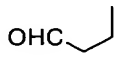
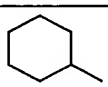
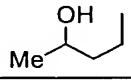
[Table 51]



Compound No.	R^r	R^5
10-138		
10-139		
10-140		
10-141		
10-142		
10-143		
10-144		
10-145		
10-146		
10-147		
10-148		
10-149		

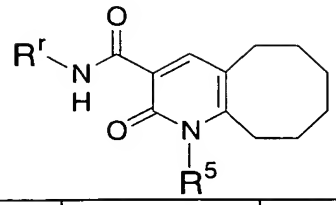
[Table 52]

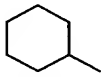
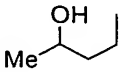
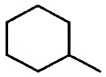
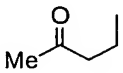
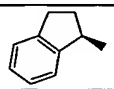
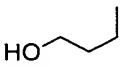
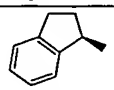
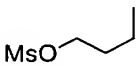
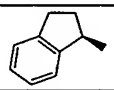
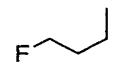
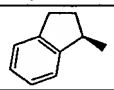
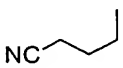
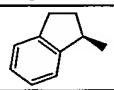
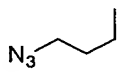
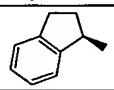
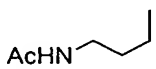
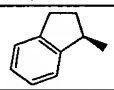
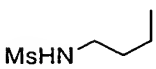
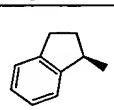
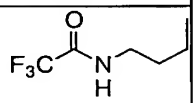
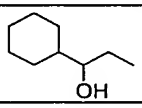
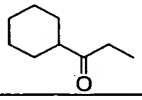
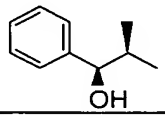


Compound No.	R^r	R^5
10-150		
10-151		nBu
10-152		nBu
10-153		
10-157		
10-158		
10-159		
10-160		
10-161		
10-162		nBu
10-163		nBu
10-164		
10-165		

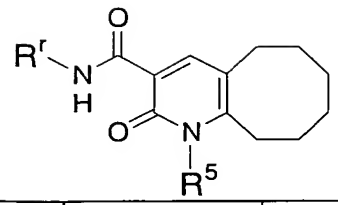
5

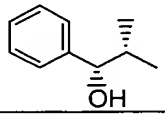
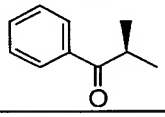
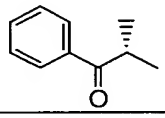
[Table 53]



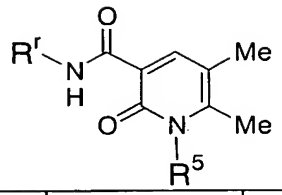
Compound No.	R^r	R^5
10-165		
10-166		
10-167		
10-168		
10-169		
10-170		
10-171		
10-172		
10-173		
10-174		
10-175		nBu
10-176		nBu
10-177		nBu

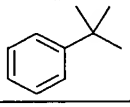
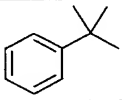
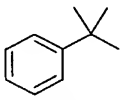
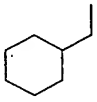
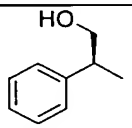
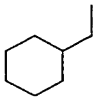
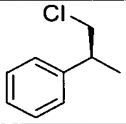
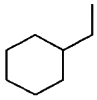
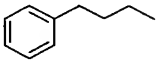
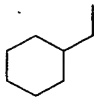
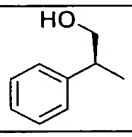
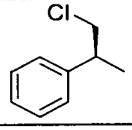
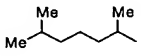
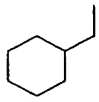
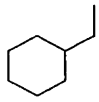
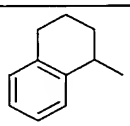
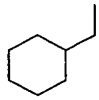
[Table 54]



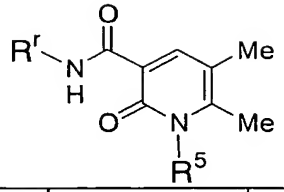
Compound No.	R^r	R^5
10-178		nBu
10-179		nBu
10-180		nBu

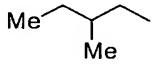
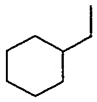
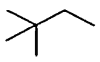
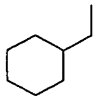
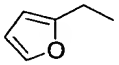
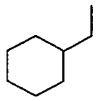
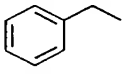
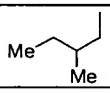
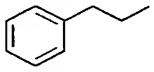
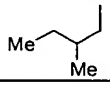
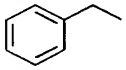
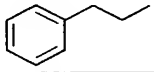
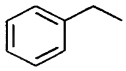
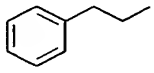
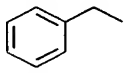
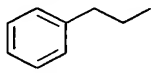
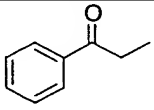
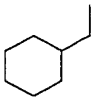
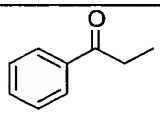
[Table 55]



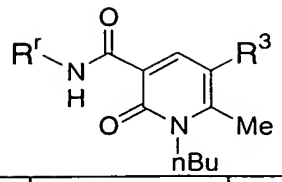
Compound No.	R^r	R^5
11-001		nBu
11-002		Bn
11-003		
11-004		
11-005		
11-006		
11-007		nBu
11-008		nBu
11-009		
11-010		
11-011		

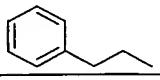
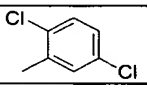
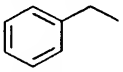
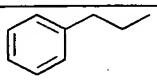
[Table 56]



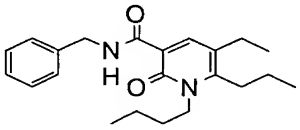
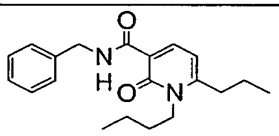
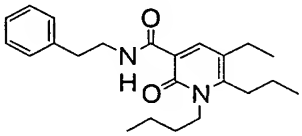
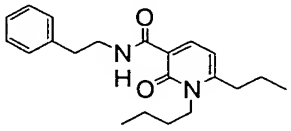
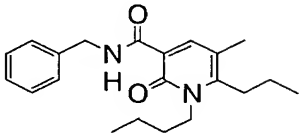
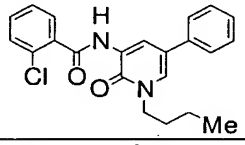
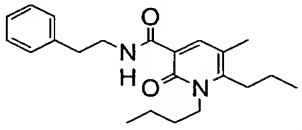
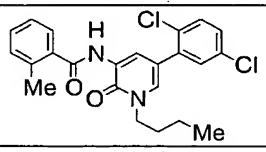
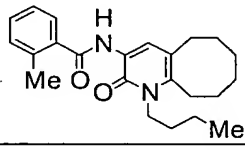
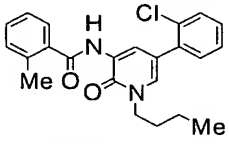
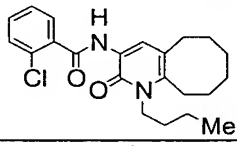
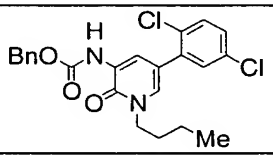
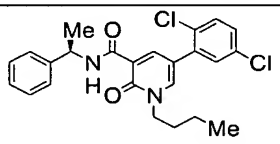
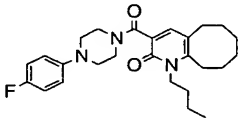
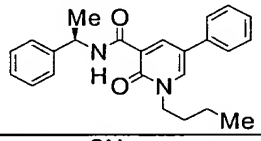
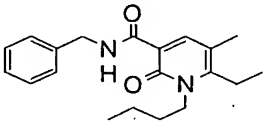
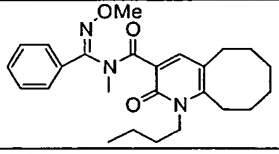
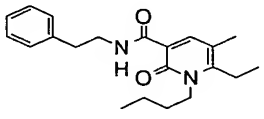
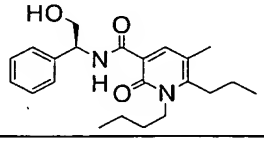
Compound No.	R^r	R^5
11-012		
11-013		
11-014		
11-015		
11-016		
11-017		
11-018		
11-019		
11-020		
11-021		
11-022		
11-023	H	nBu
11-024		
11-025		Bn

[Table 57]

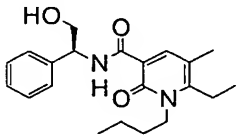
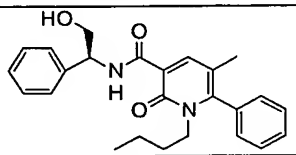
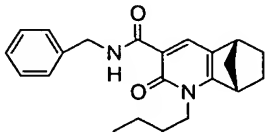
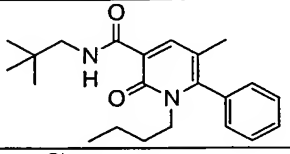
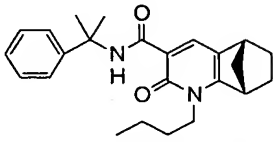
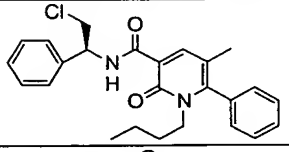
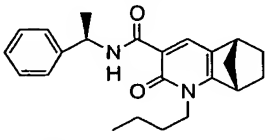
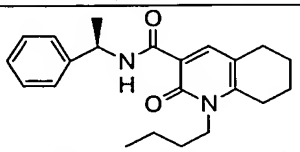
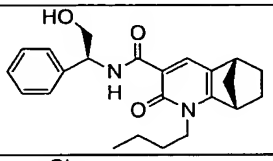
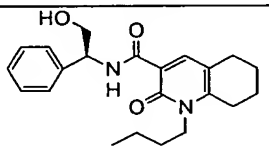
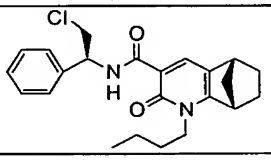
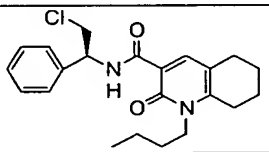
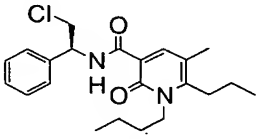
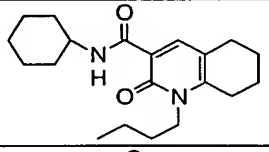
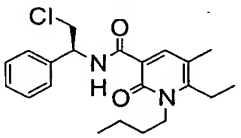
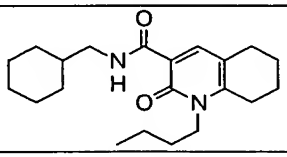
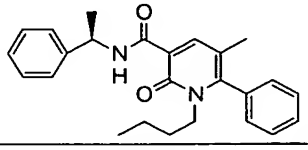
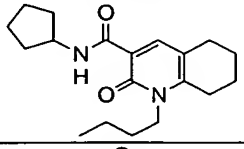
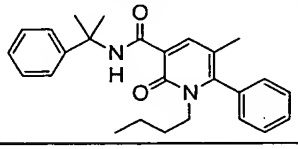
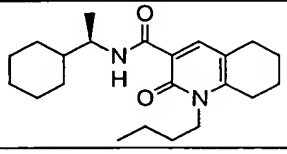


Compound No.	R^r	R^3
12-001		
12-003		Et
12-004		Et

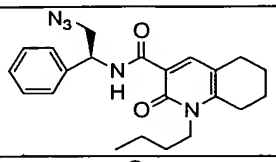
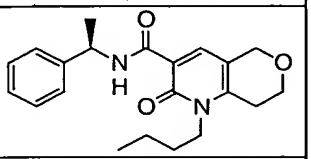
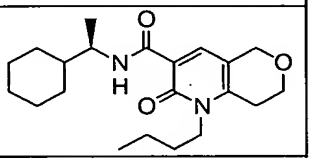
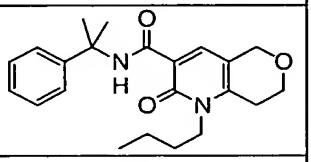
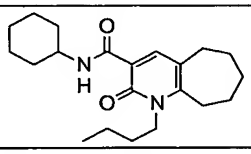
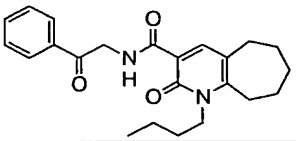
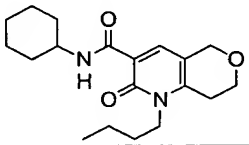
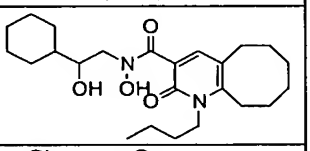
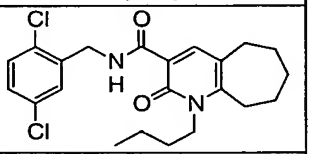
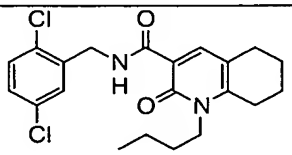
[Table 58]

Compound No.	Structure	Compound No.	Structure
13-001		13-011	
13-002		13-012	
13-003		13-013	
13-004		13-014	
13-005		13-015	
13-006		13-016	
13-007		13-017	
13-008		13-018	
13-009		13-019	
13-010		13-020	

[Table 59]

Compound No.	Structure	Compound No.	Structure
13-021		13-031	
13-022		13-032	
13-023		13-033	
13-024		13-034	
13-025		13-035	
13-026		13-036	
13-027		13-037	
13-028		13-038	
13-029		13-039	
13-030		13-040	

[Table 60]

Compound No.	Structure
13-041	
13-042	
13-043	
13-044	
13-045	
13-046	
13-047	
13-048	
13-049	
13-050	

When using a compound of the present invention in treatment, it can be formulated into ordinary formulations for oral and parenteral administration. A pharmaceutical composition containing a compound of the present invention can be in the form for oral and parenteral administration. Specifically, it can be formulated into formulations for oral administration such as tablets, capsules, granules, powders, syrup, and the like; those for parenteral administration such as injectable solution or suspension for intravenous, intramuscular or subcutaneous injection, inhalant, eye drops, nasal drops, suppositories, or percutaneous formulations such as ointment.

When the compound uesed as an active ingredient has a week cannabinoid type 1 receptor agonistic effect and a strong cannabinoid type 2 receptor agonistic effect, all kind of formulations.thereof can be used. Especially, it can be used as oral administration such as tablets, capsules, granules, powders, syrup. When the compound uesed as an active ingredient has a strong cannabinoid type 1 receptor agonistic effect, preferable is a topical administration, especially, preferable are ointment, cream, lotion, and the like.

In preparing the formulations, carriers, excipients, solvents and bases known to one ordinary skilled in the art may be used. Tablets are prepared by compressing or formulating an active ingredient together with auxiliary components. Examples of usable auxiliary components include pharmaceutically acceptable excipients such as binders (e.g., cornstarch), fillers (e.g., lactose, microcrystalline cellulose), disintegrates (e.g., starch sodium glycolate) or lubricants (e.g., magnesium stearate). Tablets may be coated appropriately. In the case of liquid formulations such as syrups, solutions or suspensions, they may contain suspending agents (e.g., methyl cellulose), emulsifiers (e.g., lecithin), preservatives and the like. In the case of injectable formulations, it may be in the form of solution or suspension, or oily or aqueous emulsion, which may contain suspension-stabilizing agent or dispensing agent, and the like. In the case of an inhalant, it is formulated into a liquid formulation applicable to an inhaler. In the case of eye drops, it is formulated into a solution or a suspension.

Although an appropriate dosage of the present compound varies depending on the administration route, age, body weight, sex, or conditions of the patient, and the kind of drug(s) used together, if any, and should be determined by the physician in the end, in the case of oral administration, the daily dosage can generally be between about 0.01 - 100 mg, preferably about 0.01 - 10 mg, more preferably about 0.1 - 10 mg, per kg body weight. In the case of parenteral administration, the daily dosage can generally be between about 0.001 - 100 mg, preferably about 0.001 - 1 mg, more preferably about 0.01 - 1 mg, per kg body weight. The daily dosage can be administered in 1 - 4 divisions.

Best Mode for Carrying Out the Invention

The compounds represented by the formula (I) can be synthesized by the preparation method described in WO 01/19807 or WO 02/072562. The compounds represented by the formula (II) can be synthesized by the preparation method described in WO 02/053543.

Example

Test example

Experimental Examples 1, 2 and 3: Effect on antigen-induced bronchial hyperresponsiveness, inflammatory cell infiltration and mucus secretion in BN rats (Acute model)

Antigen-induced bronchial hyperresponsiveness in BN rats: Brown Norway (BN) rats (Charles River Japan) were actively sensitized by the intraperitoneal injection of 1 mL mixture containing aluminum hydroxide gel (1 mg) and ovalbumin (0.1 mg, OVA). Ten days later, antigen challenge was performed by the inhalation of an aerosolized 1% OVA solution for 30 min using an ultrasonic nebulizer. ACh was intravenously injected to rats 24 h after antigen challenge under sodium pentobarbital anesthesia (80 mg/kg, i.p.) by increasing doses of ACh every 5 min, then bronchoconstrictor response observed immediately after each ACh injection was measured by the method of Konzett &

Rössler with some modifications. Briefly, trachea of rats was incised and a cannula was attached to lung side. An artificial respirator (SN-480-7, Shinano) was connected to the cannula, and then a fixed amount of air (tidal volume: 3 mL, ventilation frequency: 60 times/min) continuously insufflated to maintain respiration. The insufflation pressure overflowed from inhalation tube was monitored by a pressure transducer (TP-400T, Nihon Kohden) and recorded on a recorder (WT-645G, Nihon Kohden) through a carrier amplifier (AP-601G, Nihon Kohden). Test compounds were administered orally once 1 h before antigen challenge. The area under the curve (AUC) calculated from dose-response curve for ACh was compared between vehicle-treated control group and test compound-treated group, and then statistical significance was analyzed concerning inhibitory effect on bronchial hyperresponsiveness.

Compound I-270 exhibited a significant effect ($P<0.01$) at a dose of 100 mg/kg.

Compound 4-320 exhibited a significant effect ($P<0.01$) at a dose of 10 mg/kg.

Antigen-induced airway inflammatory cell infiltration in BN rats: After finishing experiment mentioned above, the lungs were washed 3 times with 5 mL of physiological saline through tracheal cannula using injection syringe. Then the cell number in the washing was determined. The preparations for differential cell count were prepared using Cytospin 3 (Shandon). Differential cell counts were performed after May-Grünwald-Giemsa staining, and then statistical significance was analyzed concerning inhibitory effect on airway inflammatory cell infiltration.

Compound 4-320 exhibited a significant effect ($P<0.01$) at doses of 1 and 10 mg/kg.

Compound 10-051 exhibited a significant effect ($P<0.01$) at doses of 30 and 100 mg/kg.

Antigen-induced mucus secretion in BN rats: After measurement of bronchial hyperresponsiveness, the lungs were washed 3 times with 5 mL of physiological saline through tracheal cannula using injection syringe, and then the washing was centrifuged. Mucin levels in the supernatants were measured by the method described below: 1) Microtiter plates (Immulon IV) were coated with 1000-fold diluted

supernatants diluted with phosphate buffered saline for 2 h at 37°C, and then blocked with Block-Ace. 2) Plates were washed with phosphate buffered saline containing 0.05% Tween 20 (PBST), and then incubated with 150 μL of 5 μg/mL biontinylated jacalin for 1 h at 37°C. 3) Plates were washed with PBST, and then incubated with 150 μL of a 1/500 dilution of streptavidin-conjugated alkaline phosphatase for 30 min at room temperature. 4) After a final wash with PBST, 200 μL of pNPP liquid substrate system was added. 5) Several minutes later, the reaction was stopped by adding 100 μL of 3N NaOH, and then optical densities were measured at 405 nm). Statistical significance was analyzed concerning inhibitory effect on mucus secretion.

Compound 4-320 exhibited a significant effect ($P<0.01$) at a dose of 10 mg/kg.

Experimental Examples 4, 5 and 6: Effect on antigen-induced bronchial hyperresponsiveness, inflammatory cell infiltration and mucus secretion in BN rats (Chronic model)

Antigen-induced bronchial hyperresponsiveness in BN rats: BN rats were actively sensitized by the intraperitoneal injection of a mixture containing aluminum hydroxide gel and ovalbumin. Twelve days later, antigen challenge was performed by the inhalation of an aerosolized 1% OVA solution or physiological saline for 30 min using an ultrasonic nebulizer (NE-U12, Omron). To establish chronic bronchial hyerreactivity model, this procedure was repeated 3 times with 1-week intervals. Test compounds were administered orally for 8 days from the day of third antigen challenge. On the day of third antigen challenge, test compounds were administered 1 h before challenge. One hour after last administration of test compounds, forth antigen challenge was performed. Inhibitory effect on bronchial hyperresponsiveness was evaluated 24 h after last antigen challenge by the method described in the section of Experimental Example 1.

Compound I-12 exhibited a significant effect at doses of 30 ($P<0.01$) and 100 mg/kg ($P<0.05$).

Compound 4-320 exhibited a significant effect ($P<0.01$) at a dose of 3 mg/kg.

Antigen-induced airway inflammatory cell infiltration in BN rats: After finishing experiment mentioned above, the lungs were washed 3 times with 5 mL of physiological saline through tracheal cannula using injection syringe. Then the cell number in the washing was determined. The preparations for differential cell count were prepared using Cytospin 3 (Shandon). Differential cell counts were performed after May-Grünwald-Giemsa staining, and then statistical significance was analyzed concerning inhibitory effect on airway inflammatory cell infiltration as in the section of Experimental Example 2.

Compound I-12 exhibited a significant effect ($P<0.01$) at a dose of 100 mg/kg.

Compound 10-051 exhibited a significant effect ($P<0.05$) at doses of 3 and 30 mg/kg.

Antigen-induced mucus secretion in BN rats: After measurement of bronchial hyperresponsiveness, the lungs were washed 3 times with 5 mL of physiological saline through tracheal cannula using injection syringe, and then the washing was centrifuged. Mucin levels in the supernatants were measured by the method described below: 1) Microtiter plates (Immulon IV) were coated with 1000-fold diluted supernatants diluted with phosphate buffered saline for 2 h at 37°C, and then blocked with Block-Ace. 2) Plates were washed with phosphate buffered saline containing 0.05% Tween 20 (PBST), and then incubated with 150 μL of 5 μg/mL biontinylated jacalin for 1 h at 37°C. 3) Plates were washed with PBST, and then incubated with 150 μL of a 1/500 dilution of streptavidin-conjugated alkaline phosphatase for 30 min at room temperature. 4) After a final wash with PBST, 200 μL of pNPP liquid substrate system was added. 5) Several minutes later, the reaction was stopped by adding 100 μL of 3N NaOH, and then optical densities were measured at 405 nm). Statistical significance was analyzed concerning inhibitory effect on mucus secretion.

Experimental Examples 7, 8 and 9: Effect on antigen-induced bronchial hyperresponsiveness, inflammatory cell infiltration and mucus secretion in guinea pigs (Acute model)

Antigen-induced bronchial hyperresponsiveness in guinea pigs: Guinea pigs (Charles

River Japan) held in an exposure chamber were actively sensitized by the inhalation of an aerosolized 1% OVA solution for 10 min using an ultrasonic nebulizer (NE-U12, Omron) twice with an interval of 1 week. One week later, antigen challenge was performed by inhalation of an aerosolized 1% OVA generated by an ultrasonic nebulizer for 5 min. Test compounds were administered orally 1 h before antigen challenge. In addition, guinea pigs were treated with diphenhydramine (10 mg/kg, i.p.), an antihistamine, to protect the animals from anaphylactic death 10 min before antigen challenge. ACh was intravenously injected to guinea pigs 24 h after antigen challenge under urethane anesthesia (1.4 g/kg, i.p.) by increasing doses of ACh every 5 min, then bronchoconstrictor response observed immediately after each ACh injection was measured by the method of Konzett & Rössler with some modifications. Briefly, trachea of guinea pigs was incised and a cannula was attached to the lung side. An artificial respirator (SN-480-7, Shinano) was connected to the cannula, and then a fixed amount of air (tidal volume: 4 mL, ventilation frequency: 60 times/min) continuously insufflated to maintain respiration. The insufflation pressure overflowed from inhalation tube was monitored by a pressure transducer (TP-400T, Nihon Kohden) and recorded on a recorder (WT-645G, Nihon Kohden) through a carrier amplifier (AP-601G, Nihon Kohden). The area under the curve (AUC) calculated from dose-response curve for ACh was compared between vehicle-treated control group and test compound-treated group, and then statistical significance was analyzed concerning inhibitory effect on bronchial hyperresponsiveness.

Compound I-12 exhibited a significant effect ($P<0.05$) at a dose of 10 mg/kg.

Compound 4-320 exhibited a significant effect at doses of 1 ($P<0.01$) and 10 mg/kg ($P<0.05$).

Antigen-induced airway inflammatory cell infiltration in guinea pigs: After finishing experiment mentioned above, the lungs are washed 3 times with 10 mL of physiological saline through tracheal cannula using injection syringe. Then the cell number in the washing was determined. The preparations for differential cell count were prepared using Cytospin 3 (Shandon). Differential cell counts were performed after May-

Grünwald-Giemsa staining, and then statistical significance was analyzed concerning inhibitory effect on airway inflammatory cell infiltration.

Compound I-12 exhibited a significant effect ($P<0.05$) at a dose of 10 mg/kg.

Compound I-270 exhibited a significant effect ($P<0.05$) at a dose of 10 mg/kg.

Compound 4-320 exhibited a significant effect at doses of 1 ($P<0.05$) and 10 mg/kg ($P<0.01$).

Compound 10-051 exhibited a significant effect ($P<0.05$) at a dose of 30 mg/kg.

Antigen-induced mucus secretion in guinea pigs: After measurement of bronchial hyperresponsiveness, the lungs are washed 3 times with 10 mL of physiological saline through tracheal cannula using injection syringe, and then the washing was centrifuged. Mucin levels in the supernatants were measured by the method described below: 1) Microtiter plates (Immulon IV) were coated with 1000-fold diluted supernatants diluted with phosphate buffered saline for 2 h at 37°C, and then blocked with Block-Ace. 2) Plates were washed with phosphate buffered saline containing 0.05% Tween 20 (PBST), and then incubated with 150 μL of 5 μg/mL biontinylated jacalin for 1 h at 37°C. 3) Plates were washed with PBST, and then incubated with 150 μL of a 1/500 dilution of streptavidin-conjugated alkaline phosphatase for 30 min at room temperature. 4) After a final wash with PBST, 200 μL of pNPP liquid substrate system was added. 5) Several minutes later, the reaction was stopped by adding 100 μL of 3N NaOH, and then optical densities were measured at 405 nm). Statistical significance was analyzed concerning inhibitory effect on mucus secretion.

Experimental Examples 10, 11 and 12: Effect on antigen-induced bronchial hyperresponsiveness, inflammatory cell infiltration and mucus secretion in guinea pigs (Chronic model)

Antigen-induced bronchial hyperresponsiveness in guinea pigs: Guinea pigs held in an exposure chamber were actively sensitized by the inhalation of an aerosolized 1% OVA solution for 10 min using an ultrasonic nebulizer (NE-U12, Omron) twice with an interval of 1 week. One week and 2 weeks later, antigen challenge was performed twice

by inhalation of an aerosolized 1% OVA generated by an ultrasonic nebulizer for 5 min. Test compounds were administered orally for 8 days from the day of first antigen challenge. On the day of each antigen challenge, test compounds were administered 1 h before challenge. Guinea pigs were also treated with diphenhydramine (10 mg/kg, i.p.), an antihistamine, to protect the animals from anaphylactic death 10 min before each antigen challenge. Inhibitory effect on bronchial hyperresponsiveness was evaluated 24 h after last antigen challenge by the method described in the section of Experimental Example 7. The area under the curve (AUC) calculated from dose-response curve for ACh was compared between vehicle-treated control group and test compound-treated group, and then statistical significance was analyzed concerning inhibitory effect on bronchial hyperresponsiveness.

Compound I-12 exhibited a significant effect ($P<0.05$) at a dose of 30 mg/kg.

Antigen-induced airway inflammatory cell infiltration in guinea pigs: After finishing experiment mentioned above, the lungs are washed 3 times with 10 mL of physiological saline through tracheal cannula using injection syringe. Then the cell number in the washing was determined. The preparations for differential cell count were prepared using Cytospin 3 (Shandon). Differential cell counts were performed after May-Grünwald-Giemsa staining, and then statistical significance was analyzed concerning inhibitory effect on airway inflammatory cell infiltration.

Compound I-12 exhibited a significant effect ($P<0.01$) at a dose of 30 mg/kg.

Antigen-induced mucus secretion in guinea pigs: After measurement of bronchial hyperresponsiveness, the lungs are washed 3 times with 10 mL of physiological saline through tracheal cannula using injection syringe, and then the washing was centrifuged. Mucin levels in the supernatants were measured by the method described below: 1) Microtiter plates (Immulon IV) were coated with 1000-fold diluted supernatants diluted with phosphate buffered saline for 2 h at 37°C, and then blocked with Block-Ace. 2) Plates were washed with phosphate buffered saline containing 0.05% Tween 20 (PBST), and then incubated with 150 μL of 5 μg/mL biontinylated jacalin for 1

h at 37°C. 3) Plates were washed with PBST, and then incubated with 150 μL of a 1/500 dilution of streptavidin-conjugated alkaline phosphatase for 30 min at room temperature. 4) After a final wash with PBST, 200 μL of pNPP liquid substrate system was added. 5) Several minutes later, the reaction was stopped by adding 100 μL of 3N NaOH, and then optical densities were measured at 405 nm). Statistical significance was analyzed concerning inhibitory effect on mucus secretion.

Compound I-12 exhibited a significant effect ($P<0.01$) at a dose of 30 mg/kg.

Experimental Exanmple 13: Bronchodilating effect in guinea pigs

Under urethane anesthesia (1.4 g/kg, i.p.), ACh was intravenously injected to guinea pigs by increasing doses of ACh every 5 min, then bronchoconstrictor response observed immediately after each ACh injection was measured by the method of Konzett & Rössler with some modifications. Briefly, trachea of guinea pigs was incised and a cannula was attached to the lung side. An artificial respirator (SN-480-7, Shinano) was connected to the cannula, and then a fixed amount of air (tidal volume: 4 mL, ventilation frequency: 60 times/min) continuously insufflated to maintain respiration. The insufflation pressure overflowed from inhalation tube was monitored by a pressure transducer (TP-400T, Nihon Kohden) and recorded on a recorder (WT-645G, Nihon Kohden) through a carrier amplifier (AP-601G, Nihon Kohden). Test compounds were administered orally 1 h before ACh injection, then the effect on the dose-response curve of ACh was examined. Statistical significance was analyzed concerning broncohdilating effect in guinea pigs.

Compound 4-320 exhibited a significant effect ($P<0.01$) at a dose of 10 mg/kg.

Formulation example

The following formulation examples 1 to 8 are provided to further illustrate formulation example and are not to be construed as limiting the scope of the present invention. The term "an active ingredient" means a compound of the present invention, a tautomer, a prodrug, a pharmaceutical acceptable salt, or a solvate thereof.

Formulation example 1

Hard gelatin capsule are prepared using the following ingredients.

		Dosage (mg/capsule)
Ingredients	An actve ingredient	250
	Starch (dry)	200
	Magnesium stearate	10
	Total	460 mg

Formulation 2

Tablets are prepared using the following ingredients.

		Dosage (mg/tablet)
Ingredients	An actve ingredient	250
	Cellulose (microcrystalline)	400
	Silicon dioxide (fume)	10
	Stearic acid	5
	Total	665 mg

These ingredients are mixed and condensed to prepare tablets of 665 mg.

Formulation 3

Aerosol solutions are prepared using the following ingredients.

		Weight
Ingredients	An actve ingredient	0.25
	Ethanol	25.75
	Properanto 22 (chlorodifluorometahne)	74.00
	Total	100.00

An active ingredient and ethanol are mixed, and the mixture is added into a part of properanto 22, cooled at -30 °C, transferred to packing equipment. The amount needed is provided to stainless steel vessel, diluted with residual properanto 22. The

bubble unit is insalled to vessel.

Formulation 4

Tablets containig an active ingredient 60 mg are prepared as folows.

Ingredients	An active ingredient	60 mg
	Starch	45 mg
	Microcrystal cellulose	35 mg
	Polyvinylpyrrolidone (10% aqueous solution)	4 mg
	Carboxymethyl starch sodium salt	4.5 mg
	Magnesium stearate	0.5 mg
	Talc	1 mg
		150 mg

An active ingredient, Starch, and cellulose are made pass through a No.45 mesh U.S. sieve and then mixed sufficiently. The resulting mixture is mixed with a polyvinylpyrrolidone aqueous solution, made pass through a No.14 mesh U.S. sieve. The obtained granule is dried at 50 °C, made pass through a No.18 mesh U.S. sieve. To the granule are added carboxymethyl starch-Na, Magnesium stearate, and talc made pass through a No.60 mesh U.S. sieve, and the mixture was mixed. The mixed powder is compressed by tableting equipment to yield tablets of 150 mg.

Formulation 5

Capsuls containig an active ingredient 80 mg are prepared as folows.

Ingredients	An active ingredient	80 mg
	Starch	59 mg
	Microcrystal cellulose	59 mg
	Magnesium stearate	2 mg
	Total	200 mg

An active ingredient, Starch, cellulose, and magnesium stearate are mixed, made pass through a No.45 mesh U.S. sieve, and then packed to hard gelatin capsuls at amount of 200 mg/capsul.

Formulation 6

Suppository containig an active ingredient 225 mg are prepared as folows.

Ingredients	An active ingredient	225 mg
	Saturated fattyacid glyceride	2000 mg
	Total	2225 mg

An active ingredient is made pass through a No.60 mesh U.S. sieve, suspended in saturated fattyacid glyceride dissolved by heating at a minimum of necessity. The mixture is cooled in the mould of 2mg.

Formulation 7

Suspension containig an active ingredient 50 mg are prepared as folows.

Ingredients	An active ingredient	50 mg
	Carboxymethylcellulose sodium salt	50 mg
	Syrupus	1.25 mL
	Benzoic acid solution	0.10 mL
	Aroma chemical	q.v.
	Pigmentum	q.v.
	Water	
	Total	5 mL

An active ingredient is made pass through a No.60 mesh U.S. sieve, mixed with carboxymethylcellulose sodium salt and to prepare smoothly paste. To the mixture are benzoic acid solution and syrupus which are diluted with a part of water, and the mixture is stirred. To the mixture is residual water to prepare necessary volume.

Formulation 8

Intravenous formulations are prepared as follows.

Ingredients	An active ingredient	100 mg
	Saturated fattyacid glyceride	1000 ml

Usually a solution of ingredients above described is administered intravenously to a patient by the speed of 1 ml/min.

Industrial Applicability

It was found that thiazine derivatives and pyridone derivatives having cannabinoid receptor agonistic acitivity exibit the effect as an inhibitor for inflammatory cell infiltration in the respiratory tract, an inhibitor for hyperirritability in the respiratory tract, a muciparous inhibitor, or a bronchodilator.